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DUR

UNIVERSITY OF TORONTO MEDICAL JOURNAL

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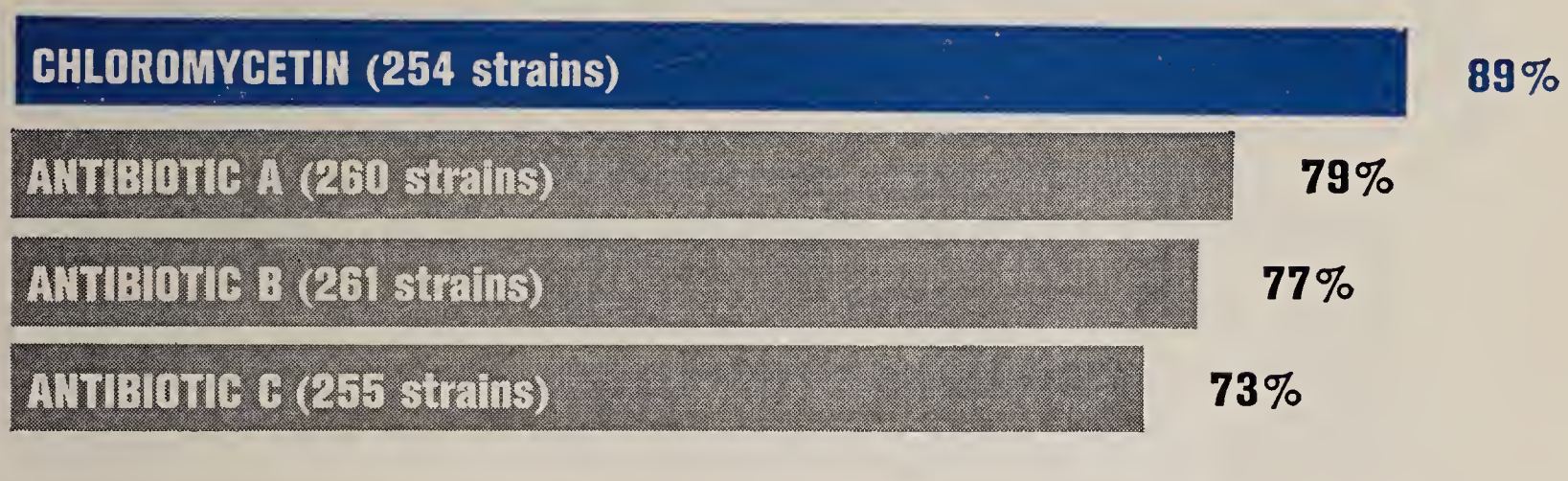

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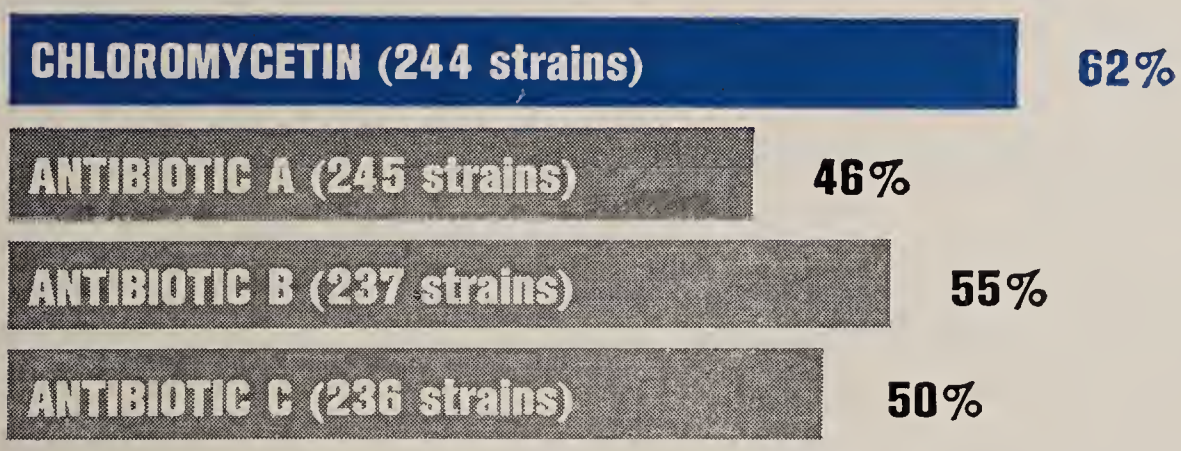

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(1) Ford, R. V., Amer. Heart J. (In Press).
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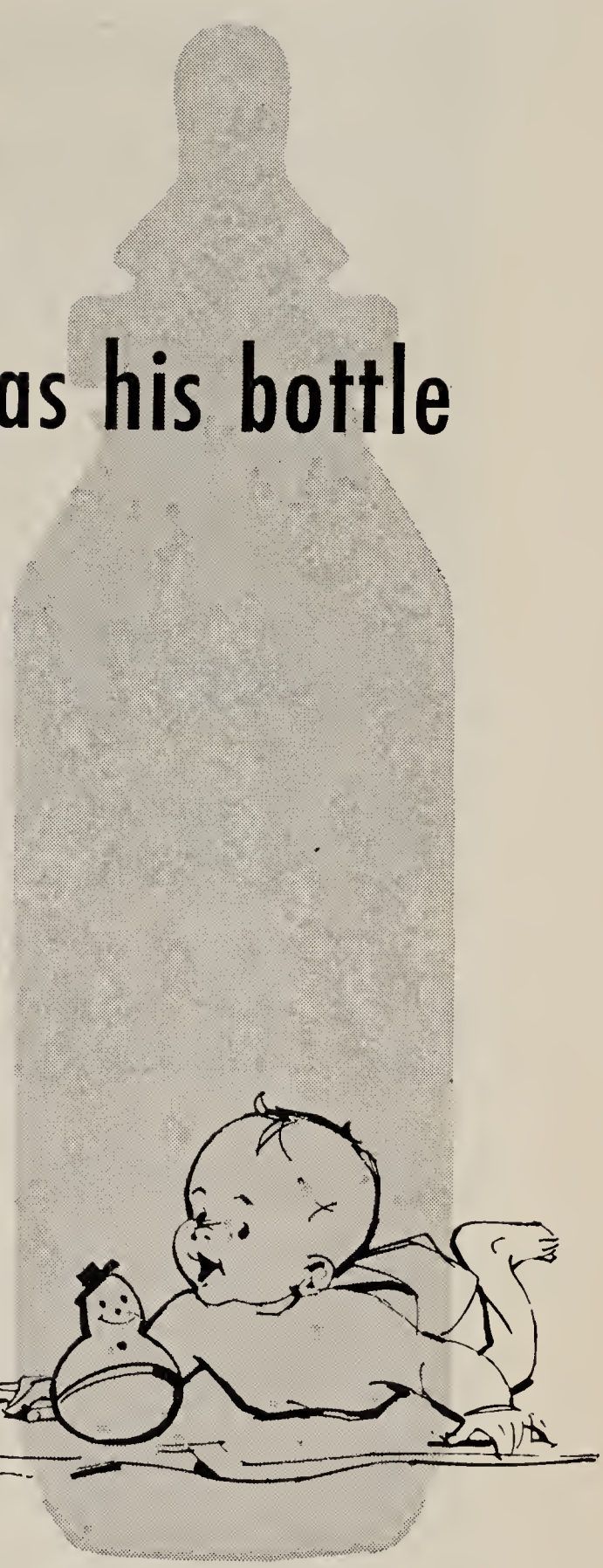

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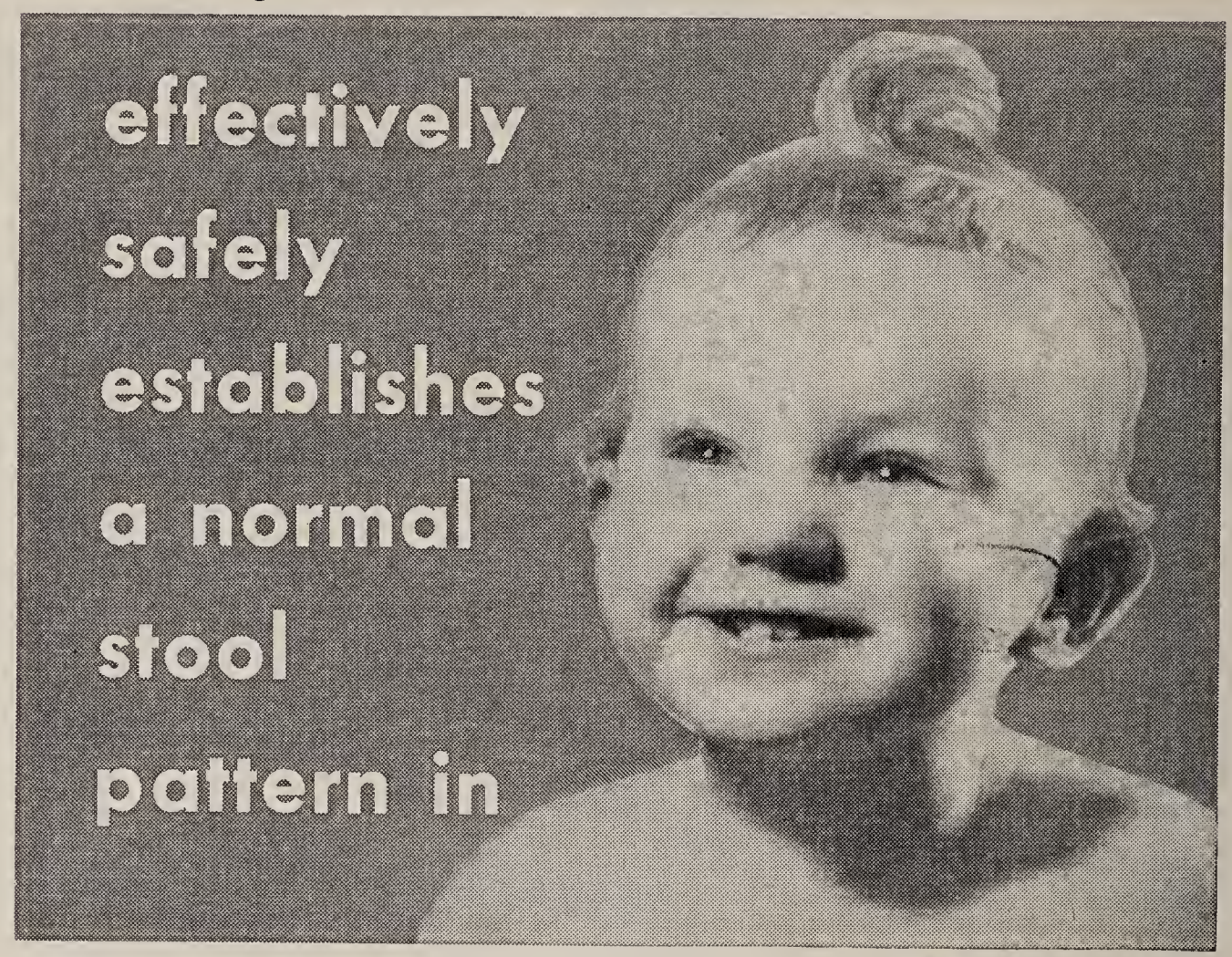

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EDITORIAL

A Glaring Fault

The Toronto General Hospital is the centre of medical education in this city. It has the greatest number of teaching beds, the largest out-patient department and the best research facilities . . . but it has no library available for senior medical students and internes as do most of the other teaching hospitals. What about the Banting Institute's library? This library has many of the latest journals but it is far from complete. It has few if any of the latest clinical textbooks and its facilities are limited. What about the University Library? Of course this library is complete but it is not convenient, for example, for the student who has three quarters of an hour to study a journal review or to read up on a difficult case. We cannot understand how such a deficiency could remain undiagnosed for so long and, if it has been diagnosed, why it has not been treated.

Medical Research at University of Toronto

In the first articles of this series a general outline of some of the more basic medical research was presented and discussed. This issue will survey briefly a few of the research projects which have a more immediate clinical application. Clinical research teams are extremely active in all the teaching hospitals and it is from their tireless efforts that the material for this issue comes.

Finale

1959–60 was the 37th year of publication of the University of Toronto Medical Journal. This year also we received a gift of the first six volumes of the Journal from an alumnus of this medical school. Some quotations from editorials in these early issues might be of interest in seeing how closely the present Journal fulfils the dreams of its originators.

". . . attempting to do something hitherto untried . . . in any medical undergraduate body on this continent. . . ." This journal was a pioneer in medical undergraduate journalism and it has led the way for other similar journals which subsequently arose across Canada. As yet we are not aware of any such publication in the United States. We are still the only undergraduate journal which is published six times a year.

". . . writing and preparation of papers should be encouraged among the students . . . to encourage in the students a more articulate spirit. . . . the Journal (should be) a more effective medium for student expression. . . . The student, also, who begins by reading his undergraduate publication will be much more likely to continue reading periodicals after graduation." The Journal has remained primarily a medium for student expression and has proven itself a valuable adjunct to basic medical education, both in the writing of articles and in learning how to use graduate medical journals, which form the mainstay of the post-graduate education of the practising physician.

"The Journal . . . will carry far afield . . . the name of the University of Toronto . . . an exchange department is a distinct prospect. . . ." This has been re-affirmed many times for our circulation department receives requests for reprints from as far away as Moscow. Our list of exchanges number nearly 200 and the exchange journals are available to the entire faculty at the University Library, Science and Medicine division.

"There are appearing . . . accounts of recent researches. . . ." A highlight of volume XXXVII was the brief but comprehensive review of medical research at the University of Toronto.

"It is only by having a wealth of material from which to select that a high standard of excellence can be maintained. . . ." Our job was not made difficult by having to read an overwhelming number of articles, however, we would have appreciated the extra work had the students been so inclined. We would like to thank all our contributors, particularly those whose work we were unable to print.

"Only by the presence of names of maturity and authority . . . can we offer sufficient excellence to our readers. . . ." It used to be the policy of the Journal staff to work in close association with faculty members, however, it was found that the busy schedule of these men failed to keep up with publication deadlines and this association disappeared. It is still customary for anyone writing a paper to do so under the guidance of an authority on the subject from the teaching staff. Also, articles by staff men have been featured in the Journal.

"The difficulty of appealing to the first two or three years is great . . . (but may) be resolved by securing a large number of contributors from them. . . ." This has been particularly emphasized this year and we feel that we have achieved some measure of success along these lines.

The aims and problems of the University of Toronto Medical Journal have not changed appreciably over the years. It has continued to be a valuable opportunity for the student, to be a risky financial venture for its sponsor, the Medical Society, and to be both a headache and a joy for the editorial staff. It is our hope that with loyal and conscientious work from future editors, with the continued patronage of its advertisers and, most important, with the laboriously solicited support of the medical undergraduate body the Journal will continue to flourish in the tradition of its founders.

We would like to thank the staff of the Journal for the time it has spent in its production and for its perseverance in what often seemed like a thankless task: L. E. Dorfman, for his advice and counsel; L. E. Soper, for many hours of arguing and proof-reading; W. N. Dale, for his labours in medical research; G. Renton, for banking our fortunes and appeasing our creditors; T. C. Gibson, for assembling and organizing our advertising; H. Walker, for thanklessly soliciting new advertising; K. Shumak, for his efficient handling of the circulation department; and the reliable editorial assistants who fill out the Journal masthead, M. Barkin, R. M. Gladstone, J. Hambley, J. Lundon and Miss J. Guest. Our best wishes go to Mr. L. E. Soper who will be editor-in-chief of Volume XXXVIII.

SCHIZOPHRENIA: A METABOLIC DISEASE?

R. G. LEE, 6T0

NOT too many years ago people afflicted with mental illness were thought to be inhabited by evil spirits and devils. Many weird and sometimes appalling methods were used in an attempt to entice these devils out from within the souls of their unfortunate hosts. There are cases on record of insane persons being lowered into a pit full of snakes with the hope of frightening the spirits out of them.

Today, at least in the civilized areas of the world, few people still profess to believe in the devil theory. But while we now know that the strange behaviour and disordered thinking of a psychotic individual is not caused by a devil or evil spirit lurking inside him, there is still no satisfactory explanation for the etiology of mental illness. Furthermore, although methods of treating the mentally ill have improved greatly over the past few years, the fact remains that diseases of the mind are for the most part incurable.

Mental disease can be classified into several types, but without a doubt the most important and the most serious is the condition known as schizophrenia. Schizophrenia means, literally, a splitting or fragmentation of the mind. Clinically the disease is characterized by a progressive withdrawal from the reality of one's environment and from personal contact with others. This is accompanied by a regression to a childlike or infantile behaviour pattern, often to such an extent that a formerly healthy young adult can become as helpless and incapable of caring for himself as a newborn infant.

At the present time one-fifth of all the hospital beds in the western world are occupied by schizophrenics. Furthermore, unlike heart disease and cancer which usually do not occur until after middle age, schizophrenia is a disease which most often makes its first appearance during the second and third decades, the most productive years of life. It is an extremely crippling disease both economically and socially. The cost borne by governments to keep these patients in institutions for long periods of time is enormous. In addition, there is still a certain stigma attached to mental illness, and the whole family suffers emotionally when one member has to be committed to a mental institution. Hoskins has summed up the situation by stating, "The problem of schizophrenia presents to the medical profession the outstanding challenge of our day."

In a century which has witnessed most of the major discoveries in the understanding and treatment of disease, why does schizophrenia still remain such a baffling mystery? Many explanations could be offered. In the first place, there is as yet no universal agreement on the definition of schizophrenia. It has recently been suggested that schizophrenia is not a single disease entity, but merely a symptom which could result from any number of different causes. Bleuler speaks of "the group of schizophrenias".

Another problem facing research workers is the difficulty of obtaining any valuable information on schizophrenia from animal experiments. In many other diseases the results of work with animals have led directly to discovering the cause and cure for the disease. Experiments have been done with extracts of schizophrenic serum and urine, injecting them into almost every species of animal including monkeys, rats, spiders, and Siamese fighting fish. While peculiar behaviour is sometimes seen in animals following these injections, it is impossible to duplicate the disorders of higher intellectual function so characteristic of schizophrenic humans. It is rather diffi-

cult to imagine a fighting fish with ambivalence or flattening of the emotions!

Finally, schizophrenia is a disorder of thought processes and content, mood, personality, and other entities which can not be measured objectively. Therefore, any reports of clinical research will inevitably have attached a certain amount of subjective bias which adds to the difficulty of sorting out the significant data.

Over the past few years a large body of evidence has accumulated to suggest that perhaps schizophrenia is something more than a mere disorder of the thoughts and emotions. And indeed, one does not have to observe many acutely ill, violently disturbed schizophrenics before entertaining the thought that these people must have some physical or organic basis for their disease. Many psychiatrists now feel that the future of research on schizophrenia lies in the field of biochemistry and metabolism. Let us now proceed to consider some of the observations and discoveries which have given support to this idea.

GENETIC FACTORS

Recent studies in the field of genetics have provided some evidence that there is a definite organic factor involved in the pathogenesis of schizophrenia. It has been observed that schizophrenia does show some tendency to run in families, and when one member of a family develops the disease, the other members seem to be more prone than the general population to become schizophrenic. In early studies on large populations, Kallman reported a remarkable correlation between the incidence of schizophrenia and the degree of consanguinity in relatives of known schizophrenics.

The overall incidence of schizophrenia is five to eight per 1000, while the incidence among siblings is 7%, or ten times the incidence among the general population. Even more remarkable are studies which have been done on monozygotic or identical twins. It has been found that when one of a pair of twins develops schizophrenia, in 85% of the cases the second twin will also develop the disease.

The chief criticism of these observations is that close relatives of schizophrenics are usually exposed to similar environmental stresses, and it cannot be denied that environment does play, at least, a partial role in the pathogenesis of schizophrenia. Few schizophrenics present with a history of having been perfectly normal and well-adjusted individuals prior to their initial breakdowns, and one does not have to study too many case histories before observing a high incidence of disrupted early home life and frequent stress situations. However, the important point to note here is that for every individual who is rejected by his parents, beaten by an alcoholic father and constantly criticized by a threatening punitive mother, and eventually goes on to develop schizophrenia, there are hundreds of other individuals who are subjected to the same environmental stresses in childhood and yet are able to cope with this and go on to live a happy, well-adjusted life. There must be some yet undiscovered mechanism at work which causes certain individuals to have a low "frustration tolerance".

The exact manner in which genetic factors are involved in the pathogenesis of schizophrenia is by no means clear. One current theory depends on the assumption that genes in some way control enzyme activity. Mutations involving certain genes could lead to abnormal enzymatic reactions in the cerebral metabolism. It has been suggested that in schizophrenic diseases the ganglion cells in the brain are altered by hereditary enzymatic anomalies.

In any case it is a rather attractive hypothesis that certain individuals are born with a weakness or disorder in their cerebral metabolism, and that with this predisposing factor environmental stresses could have a triggering or pre-

cipitating effect in bringing about the onset of schizophrenia.

THE HALLUCINOGENIC DRUGS

The belief that schizophrenia might have a biochemical basis was given strong support in 1943 with the discovery that very small amounts of the substance d-lysergic acid diethylamide (LSD) could produce profound mental alterations in man not unlike the changes which occur in acute schizophrenia. This discovery was made accidentally by the chemist, A. Hoffman, who, at the time, was working with various derivatives of lysergic acid. One day, while working in the laboratory, he was seized by a peculiar sensation of vertigo and restlessness. On returning home and lying down he experienced a state in which fantastic pictures of extraordinary plasticity and brilliant colour seemed to surge toward him.

Since that time several carefully controlled experiments have been performed giving LSD to human volunteers. In 1949 Rinkel, working in Boston, gave LSD by mouth to 100 normal volunteers as well as to a few psychotic patients. The results of this experiment showed that in general the LSD-induced mental manifestations seemed to be similar to those observed in the acute schizophrenic turmoil state. One of the common features of the LSD-induced psychosis was a dissociation of thought processes, an inability to maintain a logical, coherent train of thought. This is one of the primary manifestations of schizophrenia. Other features observed in these volunteers were an inappropriate affect, catatonic manifestations, phenomena of depersonalization, hostility, and disturbances of visual, gustatory, auditory and tactile perception. Disturbances in the function of the autonomic nervous system were present in all the LSD subjects. Moreover, as in acute schizophrenia, there did not appear to be any interference with intellectual functions, memory and consciousness. In this series active hallucinations and delusions were not frequently seen.

Subsequently other drugs such as mescaline, harmine and yohimbine were found to have similar psychotomimetic properties. It was not long before people became curious about the chemical mechanisms by which LSD and these other drugs were able to produce such interesting phenomena. These mechanisms have still not been clearly established. It has been suggested that the observed effects could be related to some alteration of oxygen utilization or carbohydrate metabolism within the brain. It has also been shown that pseudo-cholinesterase, an enzyme whose function in the brain is not yet known, but which is suspected of being involved in mental abnormalities, is inhibited by LSD. Other workers have suggested that LSD may interfere with the transmission of impulses across intracerebral synapses. Another theory suggests that there may be some interaction between LSD and 5-hydroxytryptamine (serotonin). More will be said of this later when serotonin is discussed in greater detail.

It is still much too early to draw any definite conclusions from these studies except to say that LSD is capable of producing profound mental disturbances in man. There are certain dissimilarities between the LSD-induced psychosis and clinical schizophrenia, and it is certainly wrong to state that LSD causes schizophrenia. However, the work with the hallucinogens has paved the way for further research on schizophrenia. Let us now consider some of the newer concepts which have developed in recent years.

THE TOXIC METABOLITE THEORY—ADRENALIN AND ITS DERIVATIVES

It does not seem entirely unreasonable to postulate that if a substance such as LSD can act as an exogenous toxin to produce such striking mental changes, then schizophrenia could be a state of intoxication resulting from the accumulation of an endogenous poison secondary

to some metabolic abnormality. And indeed, this idea of a toxic metabolite has been suggested by many psychiatrists. As early as 1906 Carl Jung stated his belief in an undiscovered toxine—X, a viewpoint which led to his break with Sigmund Freud, who, like most psychoanalysts of the time, believed that schizophrenia resulted from emotional difficulties in early childhood.

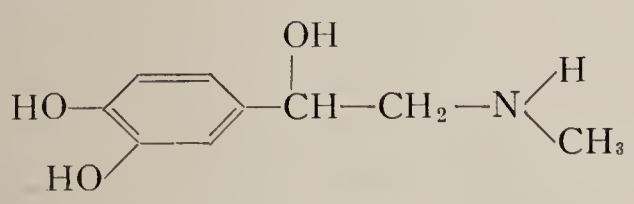
Some of the most promising research on schizophrenia and the most valid support for the toxic metabolite theory has come from within our own country. Hoffer, Osmond and their associates in Saskatoon have developed the hypothesis that schizophrenia is due to a faulty metabolism of adrenalin. They believe that in schizophrenics adrenalin metabolism is diverted along abnormal pathways resulting in products which are toxic to brain tissue thus producing the bizarre clinical manifestations of the disease.

Their work commenced in 1950 with the observation that mescaline, a hallucinogen derived from the Mexican cactus peyotl, could produce a psychotic state similar to that already described for LSD. Next, it was noted that the chemical structure of mescaline was similar to that of adrenalin. Hoffer and Osmond then suggested that there might be some naturally-occurring mescaline-like compound (M substance) formed in the body from adrenalin and capable of producing the psychotic manifestations of schizophrenia. With this background the search for the elusive M-substance was started.

The Saskatoon group received further encouragement when they learned that some asthmatics experienced certain psychotic changes after using either excessively large amounts of adrenalin or batches of adrenalin which had undergone deterioration. One asthmatic described the experience as a feeling of unreality in which he saw coloured visions before his eyes, and a sense that the outside world had become changed. Further information was contributed by another Saskatchewan doctor who remembered that during the war a deteriorated form of adrenalin, "pink adrenalin", had sometimes produced behaviour disturbances when used in anaesthesia.

In 1952 Hoffer and Osmond began experimenting with adrenochrome and adrenolutin, two closely related coloured derivatives of adrenalin. Using human volunteers including themselves, they found that the administration of these substances to normal subjects produced mental changes of a schizophrenic type such as "blocking, referential thinking, delusions, slowing of thought, lack of insight, decrease in level of abstraction, depression, often with a paranoid tinge, and changes in personality". The effects seemed to appear within one hour and usually disappeared within twelve hours. Moreover, the reaction appeared to be potentiated by the preliminary administration of a small dose of LSD.

Unfortunately, adrenochrome proved to be rather unstable and difficult to synthesize, and before long their supplies became exhausted. For a while the work



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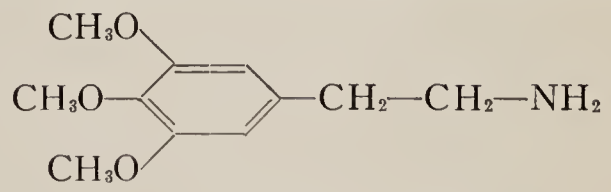

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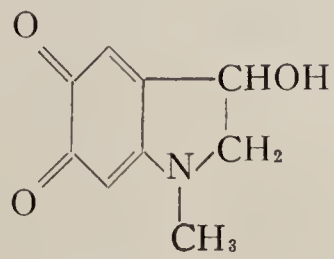

ADRENOCHROME

remained at a standstill. Eventually, however, new supplies of the compound were obtained and further tests were conducted. It was found that adrenochrome placed in the ventricles of animals in close proximity to brain tissue produced distinct behaviour disorders.

Another important step was made when Hoffer and Osmond devised a method to demonstrate the presence of adrenochrome and adrenolutin in the blood. They found no significant difference between the blood adrenochrome level of normal individuals and schizophrenics. However, it was observed that when LSD is administered to normal individuals there is a dramatic rise in blood levels of adrenochrome, and adrenochrome subsequently injected intravenously is destroyed much less rapidly. It appeared possible that schizophrenics might have some diminished capacity for removing adrenochrome from the blood.

These theories have received considerable criticism and many laboratories have had difficulty synthesizing adrenochrome and reproducing the findings of Hoffer and Osmond. Recent work on adrenalin metabolism has even failed to demonstrate the oxidation of adrenalin via adrenochrome and adrenolutin and many competent workers have been unable to demonstrate the presence of these substances in the blood of either normal individuals or schizophrenics.

However, Hoffer and Osmond have continued their studies and attempted to perfect their techniques. Just recently they have developed a new method of synthesizing a pure unstable form of adrenochrome. They have also devised a better assay method for adrenochrome so that they are now able to measure it accurately in blood, spinal fluid, and urine. So, in spite of certain difficulties encountered, the adrenalin theory still appears very promising.

When we see how this theory can be linked with stress, it becomes even more attractive, for it cannot be denied that acute schizophrenic reactions or relapses in chronic cases often appear to be precipitated by situations of severe emotional stress. We now know that stress leads to an increased level of circulating adrenalin, and if, as a result of some metabolic abnormality, this adrenalin is converted to a toxic product, it could quite easily trigger off an acute psychotic episode in a susceptible individual. Perhaps the adrenalin hypothesis will provide the all-important link between environmental factors and genetically determined biochemical constitution.

It is too early, however, to draw any definite conclusions. The elusive "M-substance" has not yet been discovered, although adrenochrome and adrenolutin possess many of the necessary qualifications. It is not unreasonable to suspect that there may be another as yet undiscovered toxic metabolite of adrenalin which might prove to be the key to the whole mystery.

CERULOPLASMIN AND TARAXEIN

Ceruloplasmin is a copper-containing alpha-globulin present in normal human serum. It is known to be a powerful oxidizing agent. It is mentioned in this article to illustrate the pitfalls which must be watched for and avoided in any type of research, and particularly in research on as vague and complicated a subject as schizophrenia.

The possibility that abnormal copper metabolism might be an etiological factor in schizophrenia was first raised when some German workers reported the finding of increased levels of copper in the serum of schizophrenics. They also demonstrated that practically all of this serum copper was present in the form of ceruloplasmin. Increased levels of ceruloplasmin were also found associated with pregnancy and a large number of unrelated diseases.

More recently Leach and Heath discovered that the *in vitro* oxidation of adrenalin was much more rapid in the presence of schizophrenic serum than

normal serum, and they attributed this fact to the higher levels of ceruloplasmin in schizophrenic blood.

Then Akerfeldt reported that there was a marked acceleration of the oxidation of N-N-dimethyl-p-phenylenediamine in the presence of schizophrenic serum (presumably due to the increased ceruloplasmin levels). He recommended this as a diagnostic test for schizophrenia. For a short while the Akerfeldt test received wide acclaim and many confirmatory reports were published.

Then it was observed that ascorbic acid could inhibit the oxidation of adrenalin and phenylenediamine. It was also pointed out that many hospitalized schizophrenics were rather poorly nourished and received inadequate amounts of ascorbic acid in their diets. Further tests were done using patients who had received well balanced diets with adequate amounts of ascorbic acid. In none of these patients was there any evidence of increased serum levels of copper or ceruloplasmin, and the oxidizing power of this serum on adrenalin was reduced to normal values. A positive Akerfeldt test could be explained entirely on the basis of a dietary deficiency of ascorbic acid; so much for one of the most remarkable, but shortest-lived diagnostic procedures for schizophrenia.

However, it would be a mistake to completely discard the ceruloplasmin theory yet. During the investigation of ceruloplasmin a group of workers at Tulane University were so impressed with the potent oxidant effects of schizophrenic serum that they postulated the presence in the blood of schizophrenics of a qualitatively different form of ceruloplasmin. This they proceeded to isolate, and after many complicated procedures, obtained a substance which they named Taraxein (from the Greek "tarassein"—to disturb). This substance was tested on monkeys and was found to produce marked behavioural and electroencephalographic changes. Then it was injected into several human volunteers (prisoners) all of whom subsequently showed temporary mental changes characteristic of schizophrenia. Five control subjects receiving a similar preparation from normal human serum showed no such symptoms. Another extensive test was performed using a psychiatric resident as a subject, and both he and the observer reported thinking and behaviour similar to that of a schizophrenic reaction.

Unfortunately, it appears that many of the rather remarkable observations made with ceruloplasmin and taraxein have been coloured by imperfectly controlled experimental conditions and subjective bias. However, this by no means completely invalidates the theories, and it is still quite possible that ceruloplasmin or some similar compound may prove to play a very important role in the etiology of schizophrenia.

SEROTONIN

For several years the name serotonin has been linked with schizophrenia. This hormone, chemically known as 5-hydroxytryptamine, is an indole amine derived from the amino acid tryptophane. It is widely distributed in both plant and animal tissues. Furthermore, it is known to be present in high concentration in the human brain, particularly in the limbic system and other areas of the brain which appear to be associated with emotional states.

Speculation that either an excess or a deficiency of serotonin might be related to mental abnormalities was first stimulated by Wooley and Shaw in 1954. They had observed that serotonin can produce contraction of smooth muscle, and they were working with antimetabolites of serotonin with the hopes that some of these compounds might be useful in the treatment of hypertension. In the course of these studies it was discovered that many serotonin antimetabolites produced mental disturbances in man and behavioural changes in animals. Furthermore, some of the ergot alkaloids such as

LSD and yohimbine, already known to be powerful hallucinogens, were found to be antimetabolites of serotonin. After making these observations Wooley and Shaw wrote:

"The demonstrated ability of such agents to antagonize the action of serotonin in smooth muscle and the finding of serotonin in the brain suggests that mental changes caused by the drugs are the result of serotonin deficiency which they induce in the brain. If this be true, then the naturally occurring mental disorders—for example, schizophrenia—which are mimicked by these drugs may be pictured as being the results of a cerebral serotonin deficiency arising from metabolic failure."

Since 1954 serotonin has been the subject of a large number of investigations, and a considerable body of information has accumulated. However, as often happens in research, additional work on a subject, rather than producing a clear picture, has tended to add to the confusion.

One important discovery was the finding that reserpine, a well-known tranquilizer, produces a profound and persistent fall in the level of serotonin in the brain. It has been suggested that this is brought about by a release of serotonin from the bound form within the brain. Another significant finding was concerned with the drug iproniazid used in the treatment of tuberculosis. Like many scientific discoveries this important piece of information was revealed accidentally when it was observed that a number of tuberculous patients being treated with iproniazid developed a toxic psychosis. Further investigation revealed that iproniazid inhibits the action of monoamine oxidase, an enzyme which normally destroys serotonin and also adrenalin. Therefore, it appears that iproniazid is capable of producing an increase in the level of serotonin in the brain, and in recent years certain monoamine oxidase inhibitors similar to iproniazid have been used successfully in the treatment of psychic depression.

In more recent studies with serotonin a number of inconsistencies have appeared. It has been shown that large doses of serotonin can produce an actual anti-serotonin effect. The original hypothesis that LSD produces mental abnormalities by inducing a serotonin deficiency in the brain has been somewhat invalidated by the finding that LSD in small doses behaves in many respects like serotonin and does not antagonize it. Moreover, it has been demonstrated that 2-bromo-lysergic acid diethylamide, an alkaloid with one and one-half times the anti-serotonin activity of LSD, does not produce any mental changes even when used in doses fifteen times larger than the hallucinogenic dose of LSD. The work with iproniazid also lost some support when it was found that isoniazid, another anti-tuberculosis drug, can produce a similar type of toxic psychosis, although it does not inhibit mono-amine oxidase and therefore should not be capable of raising the blood serotonin levels.

The whole picture has become so confusing that many investigators no longer believe that serotonin is involved in mental abnormalities, and among those who still support the serotonin hypothesis there is considerable disagreement as to whether an excess or a deficiency of serotonin is responsible for the mental changes. In his recent review of the biochemical theories of schizophrenia Kety states: "The direct evidence to support the early speculations that serotonin is involved in mental illness is meagre and contradictory." Further studies may show that serotonin does have some important function in the brain, but at present its exact role remains undefined.

SUMMARY

In the above paragraphs I have attempted to summarize some of the current theories concerned with a biochemical basis for schizophrenia. This article is by no means intended to be a complete review of the subject, and in a report of this length it has been neces-

sary to omit many of the interesting observations and theories which have been described in the recent medical literature.

At the present time there is much confusion and disagreement in the field of research on schizophrenia. However, so many different biochemical changes have been observed in schizophrenic patients, that one cannot help but feel that there must be some underlying metabolic abnormality responsible for this disease. What is needed now is a sound theory to link together all the isolated chemical abnormalities which have been observed. If we compare research on schizophrenia to the proverbial search for a needle in a haystack, we might say that at present several needles have been found and we now need a thread to join them all together.

It is far too early to predict any results, but with the increasing amount of research being done it is not unreasonable to hope that before too long schizophrenia will become a disease as responsive to treatment as tuberculosis, diabetes, and the other incurable diseases of former years.

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HYSTERIA

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HYSTERIA is a common disease known since antiquity. The Ancient Greeks though that hysteria was due to the wanderings of the womb (*hysteros*) throughout the body in search of humidity. Since Hippocrates described it, hysteria has engaged the attention of such great neurologists and psychiatrists as Charcot, Babinski, Freud, and Janet. In spite of this it still presents many puzzling aspects and as yet there is no agreement concerning its pathogenesis.

DEFINITION

Hysteria (conversion reaction, conversion hysteria) is a process whereby psychological tensions find expression through disturbances in function of the voluntary muscular or sensory apparatus or of the mind. It belongs to the group of psychoneuroses.

INCIDENCE

More than ninety per cent of hysterical patients are female. One author states

that among 740 cases of classical hysteria diagnosed over a period of eight years there was not a single male.[1] The disease usually makes its appearance at puberty, though it may not be recognized at the time. Though hysteria is said by some to occur predominantly among the less intelligent and the uneducated there is considerable doubt as to the validity of this statement.

PATHOGENESIS

From Hippocrates to Freud there have been numerous theories on the causes of hysteria, yet none of them have been universally accepted and most have been forgotten, rejected, or mentioned occasionally only for historical interest. Today it is agreed that hysteria is of psychogenic origin.

Janet thought that hysteria developed in individuals with a weak synthesis of consciousness and functional processes; stress acting on this already weakened synthesis would produce the symptoms of hysteria.

Freud explained the conversion reaction as due to an immaturity of sexual development with repression, and a consequent conflict giving rise to anxiety which then becomes expressed in a disguised way or converted into symptoms.

Today most psychiatrists agree that impulses and repressed elements in the personality produce anxiety which is then mitigated or dispelled by being converted into functional symptoms. The mechanism of this phenomenon is still obscure. An immature sexual development, or an Oedipal complex is by no means accepted as the only cause of hysteria although it may be an important factor in many cases.

The conversion of the inner conflict into functional symptoms relieves partly or wholly the anxiety experienced by the patient, thus constituting a primary gain. But the patient benefits from a secondary gain such as sympathy or dispensation from hateful work or domination. Money is an important secondary gain in cases of hysteria arising after an accident from which the patient believes himself entitled to compensation. This constitutes a variant of hysteria called Accident or Compensation Neurosis and the proportion of male patients in this group is much higher than in other types of hysteria. One must realize that the patient is not aware of the processes leading to symptoms and that he does not consciously try to bring about the achievement of gains. The hysterical patient is not a malingerer but a sick person who is unwilling and unable to disclose to herself the true nature of her illness.

SYMPTOMS

Hysteria may manifest itself in a multitude of different forms. Often the patient will present with the symptoms of a disease with which she is familiar. Three main groups of symptoms will be considered:

(1) loss of function of voluntary muscles
(2) loss or disturbance of function of somatic sensation
(3) loss or disturbance of certain mental functions.

The patient may often have symptoms from all groups. Common symptoms are paralysis of a limb, pain, anesthesia, blindness, vomiting, amnesia, fits, lumps in the throat, loss of voice, painful intercourse.

Motor disturbances are only functional; there are no demonstrable physiological or anatomical changes. There is no loss of reflexes. The symptoms are not compatible with an organic lesion in the nervous or muscular system. There is no wasting in the affected muscles, no clonus and no Babinski reaction. There is often no true loss of function but only the loss of a certain movement; other movements involving the same muscles may be performed perfectly well. Motor disturbances may also manifest themselves as convulsions, choreiform movements, tremors or tics.

Sensory disturbances can be seen in

many forms: blindness, deafness, localized areas of anesthesia, ataxia and pain. Hallucinations may occur in hysteria. Like the motor disturbances, sensory dysfunction can seldom be explained on an anatomical or physiological basis. Thus the anesthesia found in hysteria is often of the glove and stocking type, and represents a functional unit only to the patient ignorant of neuroanatomy. An hysterical neurologist, on the other hand, would present a difficult problem in diagnosis! Hysterical pain cannot be explained by postulating an organic lesion or a disturbance of physiological function. Its description is unusual, vague and the patient often shows a marked indifference to it though he insists on its incapacitating effects.

Psychological disturbances may manifest themselves as loss of memory (amnesia), twilight states, and the state of multiple personalities. Amnesia is seen in situations where the patient attempts subconsciously to blot out unpleasant memories. Examples of this were often seen during both world wars. In the twilight state the patient shows confusion and a clouding of consciousness but at the same time performs complex actions which may represent the fulfilment of wishes repressed at other times. Dual personality is another psychological disturbance in which the patient believes herself to be another person whose personality may be the very opposite of the patient's apparent one. Ganser's syndrome seen in prisoners is related to hysteria. The patient acts in the way a demented person is popularly believed to act. When asked specific questions he will give an obviously wrong answer which shows however that he has understood the question. He babbles and engages in childish actions.

DIAGNOSIS

Hysteria cannot be diagnosed on negative evidence, i.e. it cannot be diagnosed simply because investigations fail to reveal an organic lesion to account for the patient's symptoms. Positive evidence of psychological disturbances must be obtained. The hysterical patient is usually a young adult woman. She is talkative and overly friendly. She may give a history of similar symptoms occurring since puberty, never satisfactorily treated. She may show either a puzzling lack of concern for her symptoms, an attitude called *la belle indifférence*, or display them with an insistent demand for attention. The account of the symptoms is bizarre and the symptoms do not seem to fit into any recognizable pattern of organic disease. The patient often denies anxiety, assuring the physician that her personal situation would be a happy one were it not for the present disease. Closer questioning reveals a failure to develop mature relationships and stability. The patient is eager to ascribe her symptoms to an organic cause and may at first be indignant at any suggestion of psychogenic illness. Physical examination and laboratory investigations will fail to reveal any signs consistent with an organic lesion.

TREATMENT

Once a diagnosis of hysteria has been made the physician must refrain from any further laboratory investigations and repeated physical examinations even if new symptoms occur. The patient must be considered as suffering from an illness; skepticism and hostility must not be shown. The use of the word hysteria is to be avoided when talking to the patient as it has derogatory connotations to the layman. The physician must listen with sympathy to the patient's complaints but must not give the impression that he attaches undue importance to them. The patient must be encouraged from the beginning to get out of bed to resume her routine activities as soon as possible. She must not however, be accused of malingering or ill-will. Since hysterics are very suggestible, suggestion and persuasion can be used to good effect. It is best to refrain from giving

the patient any medicines, even placebos. The patient should be told the nature of her illness and an attempt made to give her insight of the basic disturbances in her personality. The depth of psychotherapy varies according to the severity of the illness, the personality and intelligence of the patient and the physician's assessment of the best possible results to be obtained. Treatment consists of two parts: one, the removal of the presenting symptoms; two, the improvement of the disturbed personality. While symptoms may be treated with relative ease, the second task is difficult, thankless and often impossible.

PROGNOSIS

Patients presenting with one symptom only, which has occurred in adult life and has been brought on by considerable stress have the best prognosis. A schizoid personality, a childish egocentric attitude, a situation in which hysterical symptoms bring the patient considerable gains and a long history of maladjustment make for a poor prognosis. Attempts have been made to assess prognosis from the nature of the presenting symptoms but this method seems to have had little success to date.

SUMMARY

Hysteria is a common disease especially prevalent in young women. Its etiology and pathogenesis are largely unknown. It gives rise to loss or disturbance of function of the voluntary motor, somatic sensory or psychological processes. Its diagnosis must be made on positive evidence. Treatment is mainly by psychotherapy. Prognosis depends greatly on the psychological make-up of the patient.

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LEONARDO ON MEDICINE

BRIAN STOCK, 6T4

THE medical contributions of Leonardo da Vinci can best be understood within the context of his biography. Most scholars fix the date of his birth at 1452, at Vinci, a small town in the Val d'Arno, Italy. He was the love-child of Ser Piero d'Antonio, a notary of the village, and a hill girl named Caterina. Ser Piero later married a noble lady of the village, and Leonardo was provisionally received into his father's home.

Leonardo was not provided with the traditional education of a notary. Whether Ser Piero wished to keep him on unequal terms with his legitimate children, or whether Leonardo gave promise of great abilities authors do not agree. But it was fortunate that Leonardo missed the formal medieval education, for, although he felt personally that it was a mark of inferiority, no facet of his roving, incandescent genius could have responded to the rote of the scholastic teachers.

Florence, the city of Lorenzo the Magnificent, was basking in the morning glow of the Renaissance when Leonardo's family moved there in 1469. Leonardo was enrolled in the workshop of Verrochio, where men like Botticelli and Lorenzo di Credi were studying art by the maxim laid down by Donatello a half century before: realism through the mirroring of nature. While working in the

bottega of Verrochio, in 1472, at the age of twenty, Leonardo became a member of the Company of Painters in Florence. This company was included in the Guild of Physicians and Apothecaries. The studies of Leonardo in Florence, however, were only preliminary to his later scientific and artistic endeavours; yet the principle of all his endeavours was clarified:

A painter will produce works of but poor quality if he takes for his guide the paintings of others; but if he learns from natural objects, he will bring forth good fruit.

"For Leonardo artistic creation represented a constant referral back to the realities of an ever-present nature." With the passage of time Leonardo devoted himself more and more to uncovering nature's secrets and less and less to painting. In the beginning all his scientific investigations were directed toward the perfection of his art. His point of difference from the other artists of his time lay in the later investigations, which were done not with a mind to any practical end, but to satisfy his desire for knowledge for its own sake.

Leonardo remained in Florence until 1483. He was then thirty-one years of age, and he was enduring the censure of a world no less practical and mercenary than our own, for he had not yet begun to earn a living. When he learned that the Duke of Milan, Ludovico Sforza, was in need of a military engineer, he eagerly sought the position.

Most of Leonardo's serious investigations in anatomy and physiology date from the Milan period, from 1483 to 1515, after which the Pope forbade further study. During this period he dissected more than thirty cadavers, making many incomparable drawings and annotations. More remarkable than the fact that his thoughts appear decades before others, are the brilliant features of the studies themselves. He broke from the tradition of Galen, who did most of his work with monkeys and dogs, and emphasized studies on humans. In all his drawings he scrutinizes not only the finer aspects of structure but also the method of function. In order to explain the action of the muscles he proposed to replace them in the skeleton with copper wire at all points of attachment. He was one of the first to inject solidified matter into hollow organs to determine their internal structure, and he used this method to wax casts of the ventricles of the brain and the orifices and valves of the heart. To study the eye he proposed to immerse the organ in egg white and boil everything to obtain a single coagulated block which could be cut through, eye and all, which anticipates by centuries the method of imbedding used in modern microscopic technique. It is insights such as these that magnify Walter Pater's comment that "the Renaissance of the fifteenth century was great rather by what it designed than what it achieved."

In general anatomy Leonardo followed Aristotle's conception of *partes similares* (Galen's *corpora similaria*, Avicenna's *membra simplicia*). He recognized the presence of eleven "simple members or mechanical instruments" in the human body, namely "cartilage, bone, nerves, veins, arteries, membranes, ligaments, tendons, skin, flesh and fat". In some of these classifications he admitted subdivisions: bone, for example, was either marrowy, spongy, hollow, or solid.

Leonardo made good observations of the skin, distinguishing epidermal and subcutaneous layers. He drew the axial skeleton well, but said little of connective tissue. Because muscular orientation was important for facial features and body shape, he devoted much study to the ratio of tendinous to fleshy portions, and he applied the basic laws of mechanics, a science in which he was perhaps the greatest genius of any age, to movement of the limbs. But he erred with the ancients in attributing muscular contractions to vital spirits flowing in the lumina of the hollow nerves.

The discovery of blood circulation has been mistakenly attributed to Leonardo by many scholars. Although he was aware of arteries and veins, and once used the term "circulation", he was not aware of the physiological connection between the motor function of the heart and the circulation of the blood. His mind was put off the right track by the analogy he insisted on seeing between the circulation of the blood in animals and the conveyance of the nutrient liquids of plants on the one hand, and the circulation of the waters in the bowels of the earth on the other.

It is ironic that the construction of the instrument whose perfection was his greatest asset, the eye, escaped him almost entirely. Although his drawings and dissections were adequate, his only important contribution was one known to Arab physicians, the variation of the diameter of the pupil in response to different intensities of light.

In most of his studies of structure, close collaboration of the anatomist and the artist can be discerned. This knowledge was later incorporated into the *Trattato della Pittura* (Treatise on Painting). However, his dissertations on physiology, "an exposition of the functions of the parts . . . observed directly on dissection", grew into a separate body of knowledge, in search of which, Leonardo nearly gave up painting.

Physiology was not an independent science in the fifteenth century. Even the word physiology, in the modern sense, was not used. During the middle ages a book entitled *Physiologus* was employed by naturalists, but it was entirely non-scientific. (The term, physiology, was first used by Albert von Haller, 1708–1777.) Leonardo used phrases like "instrumental use of the limbs" in place of the word; yet in all his writings there is evidence that he possessed the conceptual content.

Moreover, in view of his magnificent drawings, his physiological investigations have not received emphasis. Yet first and last he was an experimenter. Nature was his only unfailing authority.

One need only cite his description of the mechanics of respiration to illustrate his empirical attitude:
The substance of the lung is expansible and extendible, and it is interposed between the ramifications of the trachea . . .; and this substance interposes itself between these ramifications and the ribs of the chest, after the fashion of a soft feather bed.

From this beginning he goes on to distinguish between respiratory and residual air, and to describe the antagonistic function of the intercostal muscles, inspiratory for the external muscles, expiratory for the internal.

Leonardo's spirit of observation is shown in many conclusions shrewdly drawn from the life around him. To decide "whether the heart at its death changes position or no" he carried out a procedure that should not be unfamiliar to modern students of physiology. He noticed that when they kill pigs in Tuscany, they pierce the hearts of the pigs with an instrument called a *spillo* (borer), and that this instrument moves in the wound accordingly with the contractions and dilations of the heart. He measured the displacements of the borer, and from them calculated the displacements of the heart.

Some authors maintain that Leonardo, in failing to relate and champion, or even in some cases to interpret, his discoveries, was not a great man of science. Others contend that Leonardo, aware that some of his empirical methods were outlawed, that some of his conclusions were heresy, and that the very theme of his studies, the test of reason against accepted tradition, ran contrary to papal opinion, preferred to leave his observations unspoken.

Both positions can be reconciled. In an era of bravura, superstition and treachery, when scoundrels like Cesare Borgia were rampant and the Papacy extremely conservative, Leonardo was

compelled to use discretion in communicating his discoveries. But regarding his failures of interpretation or the commencement of one task before the completion of another, we can only seek a reason in the instability of his genius. His curiosity was unlimited as it was insatiable. He was no less concerned with hydraulics than anatomy, with philosophy than engineering, with the technique of art than metaphysical speculation. Like Aristotle before and Goethe after him he possessed a universal mind, a universal genius. As Gide has said, "the man of talent does as he wishes, the man of genius does what he can".

Leonardo was "the first to sense the bonds that connect all living things with each other and with the nature that surrounds them, and to establish some of the fundamental laws of life". Galen and his imitators had dissected only animals. The schools of Salerno, Bologna, and Padua had dissected a few human cadavers, but for limited purposes, to find the reason for an epidemic. Leonardo had purely scientific aims. "The authors", he says, "describe the eye in one way; but I find it otherwise." This is his strength, the core of his vision. This is the central reason why his personality, unconsumed by his works, has remained a source of attraction and amazement to both artists and scientists for centuries.

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SURGICAL RESEARCH AT THE UNIVERSITY OF TORONTO

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FOR the layman, one of the most exciting and dramatic fields of medicine is surgery, and the surgeon is a hero-figure familiar to everyone.

The dramatic and exciting aspects of surgery are not lost even on a medical student. He appreciates, with a layman, the heroic surgery that plucks a patient from the very sickle of the grim reaper, but sees oftener, with a clearer eye, the more pedestrian surgery that repairs function and prolongs life. What both layman and medical student may never see or learn is the breadth of research that goes on in the field of surgery, continually pushing back its frontiers.

Surgical research is very intense at the University of Toronto. Much of the work is fraught with all the imagination of an H. G. Wells and the phantasy of a Jules Verne, but each project has a grimly real object in mind: either the perfection of techniques in surgery that may prolong life, or the acquisition of knowledge that may be applied to such techniques.

Many men from various departments of surgery are engaged in research. In this article, an attempt is made to expose briefly the nature and extent of the work undertaken here. The projects of seven of the men are discussed under the headings of the five surgery departments involved: cardiovascular with Dr. R. O. Heimbecker, neurosurgical with Dr. W. Lougheed and Dr. T. P.

Morley, orthopaedic with Dr. W. R. Harris and Dr. I. Macnab, plastic with Dr. S. D. Gordon, and urologic with Dr. W. K. Kerr. The three projects connected with gastrointestinal surgery are conducted by Dr. D. J. Currie, Dr. N. T. McPhedran, and Dr. W. J. Spence. The final section is devoted to the many research projects under investigation at the Hospital for Sick Children.

CARDIOVASCULAR SURGERY

This represents one of the more famous and familiar fields of surgical research. Dr. R. O. Heimbecker, surgeon in the cardiovascular unit in the Toronto General Hospital explained how, in that unit, physicians and surgeons work together to develop new techniques and to study their application.

The investigative procedure perfected there over the past five years has been the left heart catheterization. Bjork in Sweden was the first man to catheterize the left heart successfully, and Toronto was the second center in North America to repeat the procedure. Over four hundred have been done now without a death, creating thus the best mortality record on the continent. Left-heart catheterization is helpful for pre-operative assessment of valvular heart disease when usual diagnostic procedures fail to indicate decisively whether benefit can be expected from commissurotomy.

Advances in corrective surgery for valvular and congenital heart disease have done much to stimulate progress in diagnosis. Since septal defects may be closed and deformed valves repaired by open-heart methods, pre-operative information about the exact location and the degree of stenosis or insufficiency of valves is essential. The work of the cardiovascular unit of the Toronto General Hospital has been outstanding in what is certainly a most difficult field.

Another surgical technique in which they are experimenting is the use of valve transplants for incompetent, diseased, fibrosed or ruptured heart valves, and such operations on dogs have had some success.

Still another project of research is the many applications of the heart-lung machine. It is used extensively in cardiovascular surgery, but with a heat exchanger modified by Dr. Heimbecker, it has been used successfully to create hypothermia for many regions of the body where the lowered metabolism so effected decreases appreciably the operative risk. A new application is to the treatment of tumours. For bony tumours of the tibia, for example, the circulation of the leg can be run through the heart-lung machine, and massive doses of nitrogen mustard circulated through that leg without the toxic effects seen with systemic use of this drug. Results thus far are amazing, with tumours literally melting away.

NEUROSURGERY

Two surgeons, Dr. W. Lougheed and Dr. T. P. Morley, are at work on totally different research programmes.

Dr. Lougheed has been occupied for some time in study and research on subarachnoid haemorrhage, and why people die after a berry aneurysm has ruptured into the subarachnoid space. He has tried experimentally to determine whether it is the presence of the blood itself in the subarachnoid space, a concomitant spasm of the arteries, a thrombosis of blood in the arteries, or a hydrocephalus resulting from a combination of the above conditions or any others that encompass death of the patient.

In his work with dogs, he has ruled out the presence of blood alone causing death. For one series of experiments, injecting blood into the subarachnoid space, he found that it was not blood itself that was fatal; indeed, it was well disposed of. In a present series, he is not injecting the blood but allowing the dog to pump blood under its own pressure from the femoral artery through a polyethylene tube into the subarachnoid space.

His experiments were stimulated by the experience of the neurosurgical staff over a five-year period from 1954 to 1958 in handling ruptured berry aneurysms. When the same technique of operation was used uniformly, the six-week death rate could be reduced from forty-five per cent in untreated cases to twenty-nine per cent in some conditions, and to three per cent in others, with an overall reduction to twenty-two per cent. By studying and determining the pathogenesis of subarachnoid haemorrhage, he hopes to be able again to diminish the death rate.

In a completely different field of neurosurgery, that of intracranial neoplastic disease, Dr. T. P. Morley (supported by the Ontario Cancer Treatment and Research Foundation) has been studying the tissue culture of brain tumours through a series of three extensive experiments.

The first was a morphological study of the tissue culture appearance of gliomas. From the microscopic examination of seventy gliomas in tissue culture, he found that in approximately fifty per cent of such tumours differentiation into processed cells was observed and, in the other fifty per cent, the cultures produced cells of the primitive fibroblast type. The main point of interest in this experiment was his conclusion that it is impossible to tell in advance from a knowledge of the histologic type of glioma, which way the cells will differentiate—into primitive fibroblast-like cells, or into cells with extensive process formation. Conversely, the true nature of the tumour cannot be deduced from its behaviour in culture. The processed cells are believed to be derived from glial tissue since the same extent of process formation was not seen in cultures from twenty meningiomas, nor from a variety of other intracranial tumours such as secondary carcinoma and pituitary adenoma.

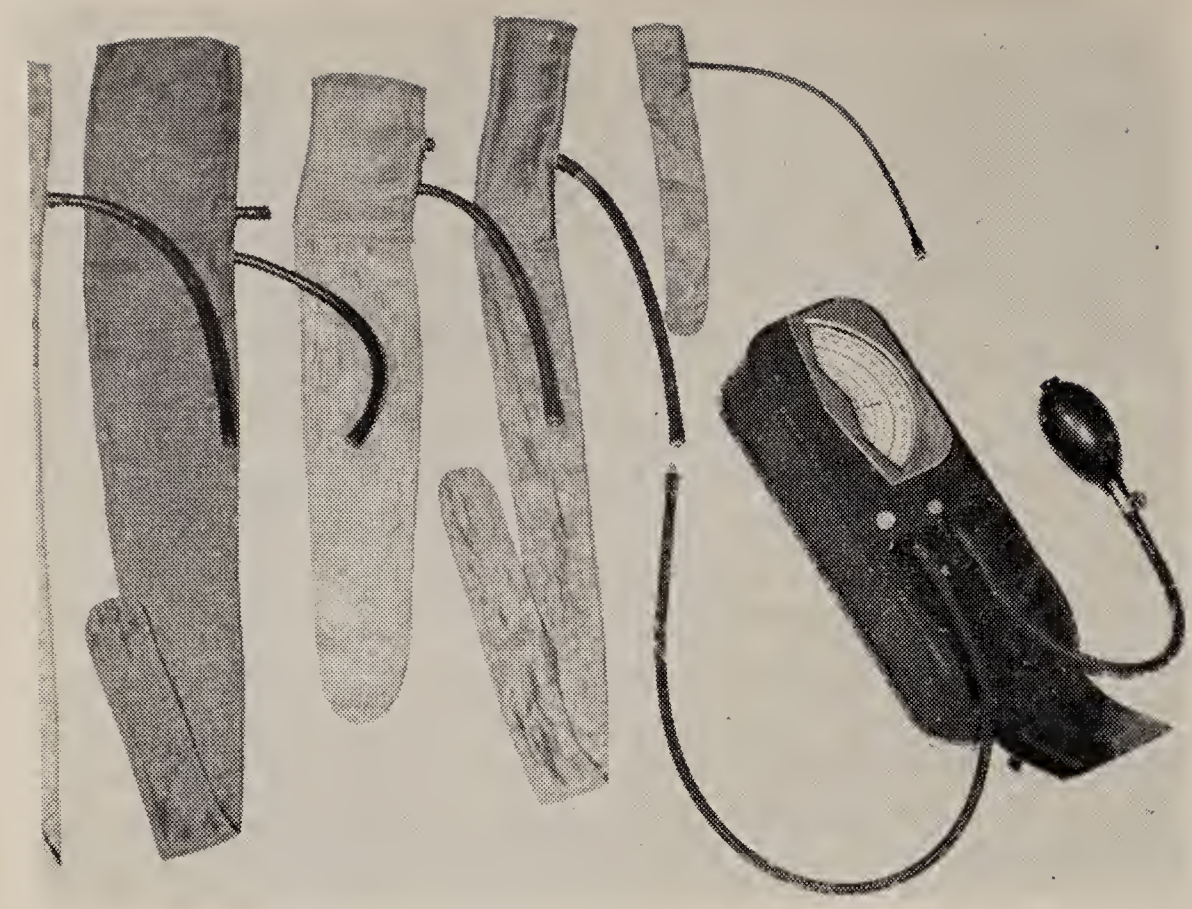
In a second series of experiments, he is attempting to determine the identity of the cells he is looking at in culture. To do this, he has tried injecting cultured cells into animals to produce a tumour, in the hope that by repeated passage through animals and culture, he could prove the true derivation of the cultured cell. Heterologous tissue, however, does not grow in the animal host. Therefore, in conjunction with Dr. Baker of the Best Institute, mice were irradiated to destroy their ability to form antibodies. (This is a standard biological experimental manipulation.) By giving a lethal dose of radiation which destroys the haemopoietic tissues, followed by a heterologous intravenous transfusion of bone marrow, the animal is kept alive by blood-forming cells that are not only from another animal and therefore of different genetic make-up, but also from another species and therefore of different chromosomal structure. Such a biological preparation is known as a *chimaera** and because of its reduced capacity to form antibodies, it is a suitable host for the transplantation of foreign tissue.

The third series of experiments (in conjunction with Dr. W. Anderson) is an attempt to recover cancer cells in peripheral blood from non-metastasizing gliomas. It seems rather contradictory that cancer cells should spread from non-metastasizing tumours and yet, from the venous blood draining the tumour bed, Dr. Morley has succeeded in recovering cancer cells singly and in clumps. They evidently spread via the blood stream, but do not take root elsewhere in the body. If there is a mechanism in the body for protection against the spread of gliomas, a study of the basis for this protection may provide an analogous method of confining other tumours in the body to their original growth site.

ORTHOPAEDIC SURGERY

In orthopaedic surgery, Dr. W. R. Harris and Dr. I. Macnab are working at long-term research projects.

*Gk. χιμαιρα = a creature with the head of a lion, the trunk of a goat, and the tail of a serpent.



CIBA

Presents

"ON INSPECTION"

J. SCHATZKER, 6T0
J. J. KAZDAN, 6T0

FIGURE 1. What is this instrument?

FIGURE 2. What do you notice?

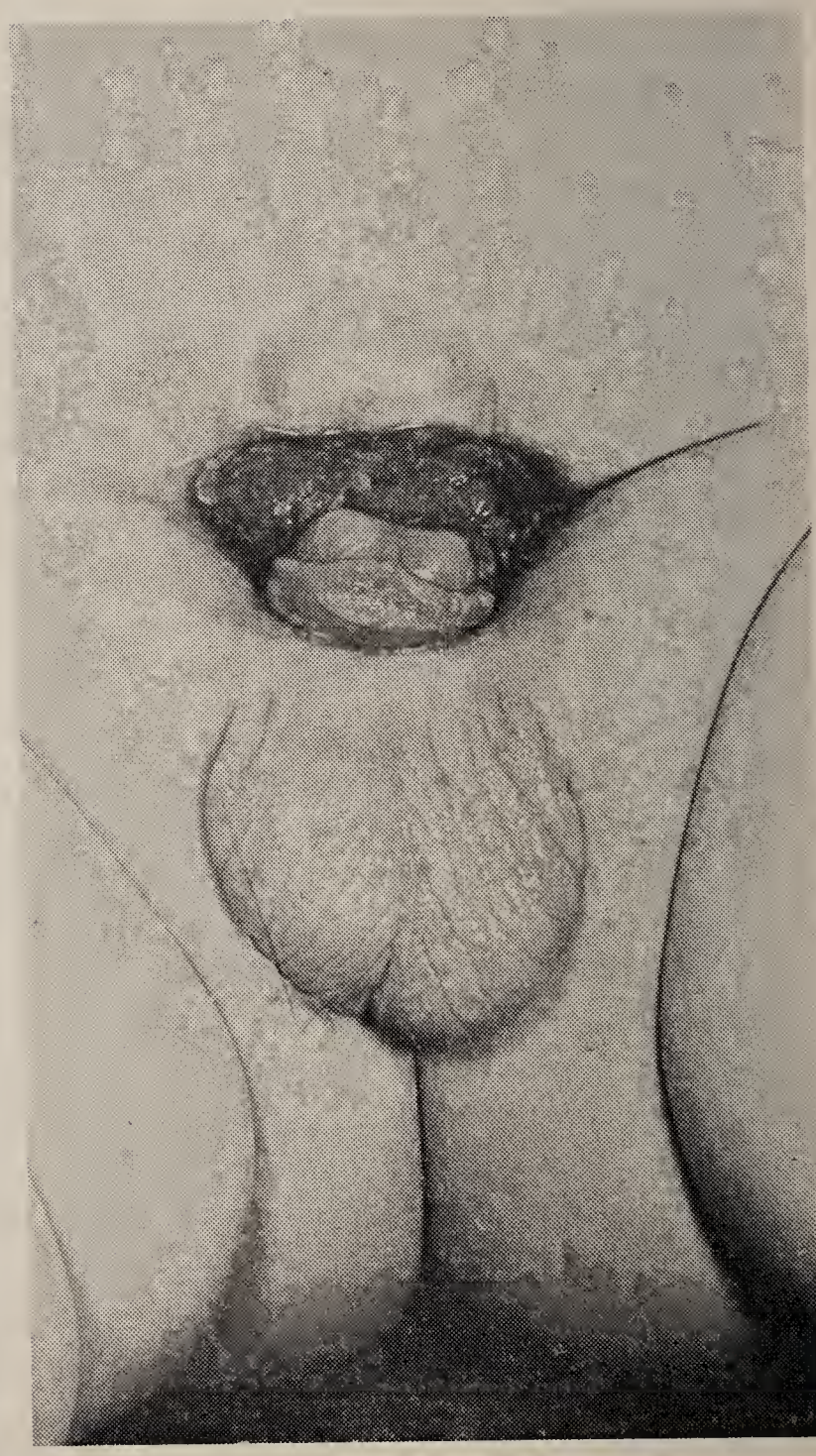


FIGURE 3. What is the name of this condition? What other anomalies are associated with it?

Answers to "On Inspection" may be found on page 195

FIGURE 4. This soft painless mass gradually developed over a 20-year period. What is your diagnosis?

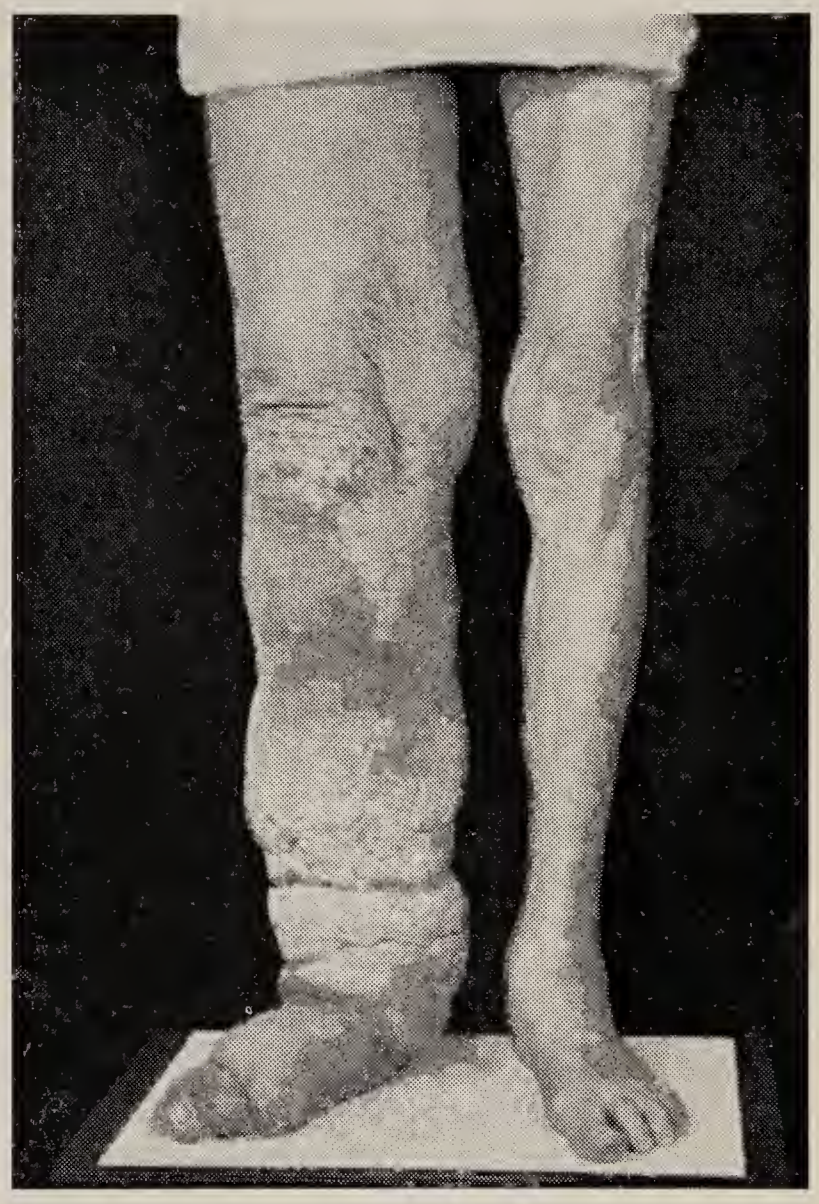


FIGURE 6. Can you name this condition? What are the commoner causes?

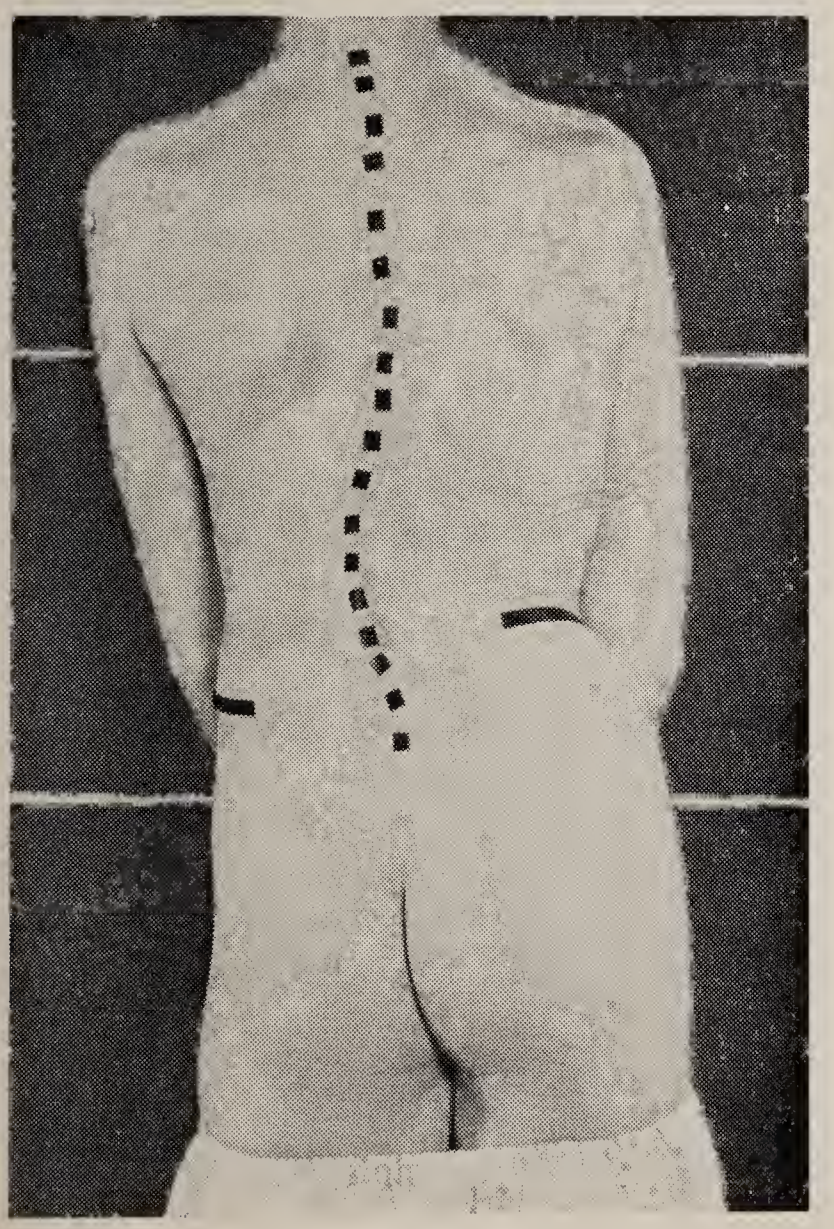


FIGURE 5. What is the name of this deformity which gradually developed in a 14-year-old girl?

One of Dr. Harris' projects is a study of fat embolism as a complication of fractures, occluding as it does the vascular system of the lungs, brain, and kidneys. Part of his study of the pathogenesis includes the injection into animals of exogenous fat, and the tracing of its course with a quartz rod microscope. By this means its distribution in the lungs can be traced and a pattern established. The continuation of this experiment is a study of the treatment of fat embolism by solvents, or by detergents (including heparin, for example) which change the electrostatic charge on fat particles. A ramification of this experiment includes the perfection of better techniques for the detection of increased fat in the blood, and the study of why serum lipase goes up after fractures, and where the fat comes from.

His second research project is a study of the role of the epiphysis and epiphyseal plates in the growth in length of long bones. The histologic features of repair after epiphyseal separation have been investigated. The growing cells remain with the epiphysis, and if the stump is wrapped in teflon, the epiphysis goes on growing. He wishes to establish whether it is the vessels in the epiphysis or the ring of vessels about it that are important for nutrition of the epiphyseal plate. He has tried to transplant epiphyseal plates and to demonstrate their subsequent growth in soft tissue and in bone as a means of stimulating growth.

This year, Dr. Macnab is studying the use of polyurethane foam in the treatment of certain types of fractures. This plastic is a substance with a tensile strength greater than bone itself and seems to be fairly well tolerated by the body. Some of the theoretical advantages of this substance are that it can be applied and moulded like a firm foam, it sets very rapidly, and finally becomes strong enough to allow the patient to use the limb without external support before the fracture is healed. However, it is still in its investigative phase and much work has to be done to establish its potentialities and dangers.

In experimental transverse fractures with the periosteum deliberately destroyed, the alignment of the bone can be maintained by a cocoon of polyurethane foam moulded around the break. This procedure, while maintaining the reduction, permits the rapid revascularization of the medullary cavity and, at the same time, prevents the ingrowth of fibrous tissue into the fracture site. Similarly, when a segment of long bone is experimentally removed, the defect can be replaced by a bone graft bonded to the defective bone with the plastic glue. In both these instances, the main function of the polyurethane foam is to act as an artificial periosteum, preventing the ingrowth of fibrous tissue between the bone ends. This, indeed, may be the chief use of the plastic and its function as a form of internal fixation may be only of secondary importance. The plastic may be used for the same purpose with bone grafts. A coating of plastic around the graft may give some form of internal fixation and, in addition, may protect the graft against invasion by fibrous tissue.

Although it is an attractive thought that broken bones and broken backs may be glued together again, the substance requires much more experimental evaluation before it can be used clinically on a wide scale.

One of the main projects in the basic research programme of the Orthopaedic Division is the problem of bone growth. In one technique employed for the investigation of this problem, a section of long bone is removed, and the broken ends are joined together by a hollow plastic tube. Various substances may be placed in the tube (blood, saline, growth hormone, homogenous and heterogenous bone chips, etc.) and the effect of these materials on the rate of bone growth can be determined.

The preliminary studies have suggested that bone growth seems to be

most rapid in the presence of dying bone in the polythene tube. This has suggested that there may be some humoral substance released by dead or dying bone promoting new bone growth. This possibility of a humoral stimulus to bone growth is being investigated further.

PLASTIC SURGERY

Dr. S. Gordon is conducting research on plastic surgical techniques in arterial replacement. In the past, major arteries have been replaced by a variety of materials from homografts of artery to many types of plastic. His own theory has been that autografts would be the best tissue and he has experimented using the patient's own dermis. Objections to this have been the dangers of infection and of cyst formation. He perfected a technique with Dr. A. Ham, formerly of the Anatomy Department, of quick-freezing and thawing a sheet of dermis three times, thus effectively killing the epithelial cells, but providing acceptable material for autogenous grafting in plastic surgery.

For two years now, Dr. Gordon has been working with Dr. J. Key of the Cardiovascular Unit in the experimental replacement of sections of dog's aorta below the renal arteries by treated dermis as an autograft. Four dogs so treated have been living now for two years, and others treated more recently are still alive and well. Three dogs were sacrificed after eighteen months, having previously had aortograms to reveal the condition of the replaced fragment. The repair results appeared very good. Histologic section showed that the tube was replaced by living fibrous tissue and elastic tissue, and lined by living endothelium.

The results of the technique show great promise in the treatment of such conditions as coarctation, aneurysm, and even arteriosclerosis.

An allied line of research followed by Dr. Gordon is a repeat study of the fate of treated dermis in rabbits. The treated dermis, surgically buried in the rabbit, is sampled at intervals over a six-month period to determine histologically the method of replacement of the dead epithelial cells with the living fibrous and elastic tissue.

Dr. Gordon's address at the International Congress of Plastic Surgeons in England last year aroused lively interest, and as the passage of time proves the effectiveness of his techniques in the laboratory animals, the application of his discoveries to human patients becomes more imminent.

UROLOGIC SURGERY

Research projects in the field of urology are conducted under Dr. W. K. Kerr. Last year an experimental study was made on the effect of radioactive colloidal gold injected into the prostate for the treatment of prostatic carcinoma. It was found that large quantities of gold escaped into the bloodstream during the first few minutes, into the urine during the first few hours, and into the lymphatics during the first few days, leaving only a small fraction of gold in the prostate. Furthermore, the volume of tissue through which the gold diffused was unpredictable. Since it would not be possible to calculate the absorbed dose, or to be assured of its even distribution, the method was not satisfactory for the definitive treatment of prostatic carcinoma.

Another study was the physiology of intestinal replacement in the urinary tract with particular reference to the use of an isolated segment of ileum to replace the bladder after cystectomy. Sodium, chloride and potassium reabsorption were determined. In the ileum or in the large bowel, there is a differential reabsorption of chloride over sodium leading ultimately to hyperchloraemic acidosis. With the ureterosigmoid transplantation (an alternative technique) this is more rapid in action and less subject to control, while in the ileocystoplasty this is slower in action and its

effects can be compensated for therapeutically.

A third project in urology is the use of renal hypothermia to protect against ischaemia in kidney operations. From the work on this project has arisen a new technique for determining the renal blood flow from the rapidity of temperature rise in the hypothermic kidney when it is reheated.

A current project is perfusion of the isolated kidney with artificially oxygenated blood in an attempt to keep it alive excreting urine. The success of this may make possible a kidney bank for kidney transplants analogous to the eye bank now so widely in use.

GASTROINTESTINAL SURGERY

Dr. D. J. Currie has been performing experiments on the pathogenesis of cholecystitis. Many workers have produced acute cholecystitis in animals by injecting seven to twenty per cent solutions of commercially prepared bile salts or doubly or triply concentrated gall bladder bile into the obstructed gall bladder. These concentrations are higher than the physiological concentrating power of the gall bladder, and so may have produced cholecystitis through chemical irritation alone. Experiments were designed to investigate the possibility that the experimental animal is able to concentrate its own bile sufficiently to produce acute cholecystitis: (a) common duct bile was transferred to the obstructed gall bladder, (b) one-way valves were implanted into the cystic duct, and (c) animals were dehydrated prior to obstruction of the cystic duct in attempts to force the concentration of bile by the gall bladder. Other experiments were planned to study the effect of sterile human gall bladder bile from surgical specimens of chronic cholecystitis on the obstructed canine gall bladder. The effect of excess sterile commercially prepared cholesterol on the dog's gall bladder was also investigated.

One hundred dogs and forty-two rabbits were used in six experiments and although no instance of acute cholecystitis was found in the absence of accidental bacterial contamination, Dr. Currie did find evidence of chronic inflammatory reactions in the gall bladders of long-surviving rabbits and in some dogs which had excess cholesterol injected into the gall bladder. Concretions of the naturally occurring bile salts (experimental gall stones) were found in long-surviving animals which had partial or complete obstruction to the outflow from the gall bladder.

Dr. N. T. McPhedran has been doing research on pancreatitis. His project is a study principally of the aetiology of the disease. In attempting to determine aetiology, one of his present experiments is representative of the type of time-consuming work that such research projects entail.

For this experiment he has taken 64 rats and divided them into four groups of 16 each. The first group gets a normal diet with fifteen per cent alcohol instead of water; the second, a normal diet with water. A third group gets a diet deficient in proteins, minerals, and vitamins (a diet which is known to produce liver cirrhosis) with fifteen per cent alcohol, while the fourth gets the deficiency diet with water. After six months, two rats per month from each group are sacrificed, and both liver and pancreas are removed for signs of cirrhosis and pancreatitis. The object is to determine whether or not a poor diet and/or alcohol can produce pancreatitis.

With this experiment, Dr. McPhedran has several others. One is an attempt to produce pancreatitis by the injection of bile under pressure into the pancreatic duct of rats. A second experiment is a check on the work of Zollinger and Elliot who claim that if a mixture of pancreatic secretion and bile is incubated at 37° for from 12 to 24 hours, and then injected at normal dog pressure (40 cm. water) into the dog's pancreatic duct, acute haemorrhagic pancreatitis

will result. Dr. McPhedran found that some but not all the animals did develop pancreatitis. A third experiment was an attempt to produce acute haemorrhagic pancreatitis by obstructing the pancreatic ducts and ligating either the pancreatic veins or the arteries. He found that obstruction of the duct alone produced mild oedematous pancreatitis, that a concomitant ligation of the veins produced chronic pancreatitis rather than the acute form, and finally that the obstruction of the duct and ligation of the arteries produced a chronic pancreatitis less marked than that produced by venous ligation.

Avenues still to be checked are the effects of obstructing the ducts and stimulating the splanchnic nerve, testing a vascular aetiology by the injection of glass beads into the coeliac artery, and investigating the possibility that acute pancreatitis may be the result of an auto-antibody reaction analogous to the Schwartzmann reaction.

Dr. W. J. E. Spence is interested in another aspect of gastrointestinal surgery: the nutrition of patients who have had various gastrointestinal diseases and operations. In his research into fat excretion in these conditions, Dr. Spence conducted his investigation with post-gastrectomy patients.

Among the post-gastrectomy patients were two groups of great concern to him: a group who lost weight before the operation and failed to regain it, and a group who lost weight after the operation. Dr. Spence and Dr. J. Finlay have tried to determine whether these conditions are due to a deficiency in caloric intake, in digestion, in absorption, or a combination of any of these.

It is impossible to know accurately the caloric intake of a patient out of hospital, while balanced against this lies the equal impossibility of keeping patients in hospital. On some, however, who had to remain in hospital because they were malnourished or for various other reasons, Dr. Spence was able to establish a base line for caloric intake, and then test their output. A sensitive test for absorption is a determination of fecal fat.

The established method of determining fecal fat content was cumbersome and unpleasant. For one and a half years, working in collaboration with Dr. Finlay, Dr. Spence tried to set up an easier method of determining fecal fat content. The method finally adopted involved the use of a radioactive iodinated oil (triolein) and a fatty acid (oleic acid). In one technique they used neutral fat with the meal, collected the stools over four days, and by using a Geiger counter on the stools, they could establish the percentage of fat absorbed. In a second technique, they took blood and plasma specimens over a six-hour period from the time of ingestion and again with the Geiger counter could establish the amount of absorption.

In synchronous combined radioactive and biochemical tests over that period, they found that some patients had steatorrhea by one test and normal fat excretion by the other. Since the old chemical method is exact, they feel that the radioactive one (which is now widely used) is not sufficiently accurate for laboratory investigation.

The establishment beyond doubt that one promising method is impracticable is often of major importance to other investigators working in the same field of research. At present, Dr. Spence is seeking another more accurate method of determining fecal fat content in the hope of reaching definite conclusions in his study of fat excretion in gastro-intestinal disease.

RESEARCH AT THE HOSPITAL FOR SICK CHILDREN

Dr. A. W. Farmer, Surgeon-in-Chief at the Hospital for Sick Children, indicated the vast breadth of research carried on at that hospital and outlined the really gigantic administrative side of research in the hospital itself which works as a

research institute under the direction of Dr. R. R. Struthers. The projects are many and varied.

Dr. Farmer with Dr. S. H. Jackson, chief biochemist, is studying burns in an attempt to determine in the blood the abnormal protein absorbed from burns.

Dr. E. B. Hendrick has initiated work on hydrocephalus, and is continuing research there in the techniques of surgical treatment for that condition.

Most of the projects are conducted by men on staff at the hospital assisted by research fellows who work one year in research.

Dr. W. T. Mustard assisted by Dr. G. Trusler and Dr. C. Bull is working at three projects in heart surgery. The first entails aortic anastomoses in puppies and is a comparison of various types of stitches and the effect of subsequent growth. This is tied in closely with the treatment of coarctation of the aorta in children. The second is a study of the function of the atria and the changes in physiology when the atria are removed. The third, in which they are assisted by Dr. J. W. A. Duckworth of the Department of Anatomy, is an attempt to stain differentially the bundle of His (the Purkinje system) since in operations for ventricular septal defects, a stitch in the Purkinje system can cause a bundle branch block.

Dr. W. K. Lindsay assisted by Dr. E. P. McDougal is studying the effect of trauma on flexor tendon function in chickens. In flexors that have had to be grafted, there is fibrosis, and they are trying to perfect a graft or primary suture. With Dr. S. Bensley of the Department of Anatomy, they are also establishing histologically the fate of free tendon grafts in chickens.

Dr. G. R. Walker assisted by Dr. R. F. Remillard is studying a new surgical approach to the treatment of portal hypertension in children. Using dogs as experimental animals, they are investigating a method to shunt blood flow from the liver and the low-pressure portal system to the low-pressure pulmonary system, and thus effectively reduce the portal hypertension.

Dr. R. B. Salter, awarded the gold medal from the Royal College of Surgeons, and Dr. D. A. Gibson are doing basic research in the effects of compression on cartilage. It was noticed that after certain orthopaedic conditions were treated, stiff joints often resulted. It was thought probable that this was due to damage to the cartilage caused by immobilization of the joint in a position in which the cartilage of the joint was compressed. Working with rabbits, it can be shown that continued compression of the articular cartilage of the knee joints leads very quickly to necrosis of that cartilage. This year they are trying to find out if degenerative arthritis is a usual sequel to such an incident. They are also attempting to determine how much pressure is required to produce necrosis of articular cartilage.

CONCLUSION

From the variety and originality of the research projects in progress, it is easily understood that, as was mentioned before, surgical research is very intense at the University of Toronto. Successful research, as all of these projects illustrate, is a combination of two essential things: the first is the idea which forms the soul of the project, and the second is the method of investigation through which the idea can be proved or disproved, and this forms the body of research. Two other necessary adjuncts are perseverance for the investigator, and money to finance everything.

In this article, only the ideas and methods in the various projects have been touched on. The perseverance and money must be inferred. The world of surgical research is a wonderland where, truly, all things seem possible.

ACKNOWLEDGMENTS

I should like to acknowledge all the assistance in the writing of this article without

which blank pages would have resulted. First I will mention the guidance of Dr. F. G. Kergin, Professor of Surgery at the University of Toronto, who directed me to the departments and research workers, active on projects in surgery. Then I must thank the men who gave unselfishly of their time and information: Dr. R. O. Heimbecker, Dr. W. Lougheed, Dr. T. P. Morley, Dr. W. R. Harris, Dr. I. Macnab, Dr. S. Gordon, Dr. W. K. Kerr, Dr. D. J. Currie, Dr. N. T. McPhedran, Dr. W. J. Spence, Dr. A. W. Farmer, Dr. D. A. Gibson, and finally Dr. C. Bull who personally guided my tottering steps through a maze of research that, without him, would have been unintelligible.

RESEARCH IN THE DEPARTMENT OF MEDICINE

W. N. DALE, 6T1

METABOLISM AND ENDOCRINOLOGY

In 1934, Goldblatt reported that hypertension could be produced in the dog by the partial constriction of the renal arteries. Since then clinicians have been searching for the human counterpart of the Goldblatt experiment with the hope of finding cases of hypertension which could be alleviated by the removal of one diseased kidney. In the first twenty years after Goldblatt's report, the results of these efforts were disappointing. Many hypertensive patients with unilateral renal disease of various types were subjected to nephrectomy and, although there were sporadic reports of success, the percentage of cures was small—in published cases less than twenty per cent. There was great diversity in the pathological findings in the kidneys so removed but most of the lesions were readily detectable by such routine investigations as intravenous or retrograde pyelography. Because of these disappointing results, clinical interest in this field tended to wane and in some centres the removal of a kidney in an attempt to cure hypertension was looked upon with disfavour.

During the past few years there has been considerable revival of interest in this subject. In 1953, Howard, Berthrong, Gould and Yendt produced evidence that, when hypertension was associated with a lesion which interfered with arterial blood flow to one kidney, there was an excellent chance of its alleviation by nephrectomy. Howard, and his associates also pointed out that routine methods of urological investigation often failed to detect such cases and demonstrated the value of differential renal function studies and abdominal aortography as diagnostic procedures. Cases of hypertension due to interference with arterial blood supply to the kidney are now being reported with increasing frequency and the results of surgical treatment in such cases have generally been good.

With these results in mind it becomes apparent that usual tests of renal function and even intravenous or retrograde pyelography may be insufficient to establish a diagnosis of renal hypertension and that in some cases further investigation is necessary before this diagnosis can be ruled out.

As the next step in the investigation of renal hypertension workers here have reported on one hundred and twenty-five hypertensive patients since 1954, on whom differential urine volume and sodium excretion studies have been performed after bilateral ureteral catheterization. This differential renal function test is based on the experimental work of White, who found in the dog, that constriction of a renal artery leads to marked reduction in the volume and sodium concentration of urine obtained from the involved kidney. In nine cases in which there has been a significant reduction in the volume and sodium concentration of

urine from one kidney, there has been confirmatory evidence of renal ischaemia either histologically or by aortography.

Yendt and his associates Drs. Kerr, Wilson and Jaworski, have been guided by the results of the differential sodium excretion studies in determining whether or not abdominal aortography, a potentially hazardous procedure, should be performed. A significant reduction in the volume and sodium concentration of the urine coming from one kidney is considered to be evidence of some renal arterial abnormality. In such cases, or when there is complete non-function of one kidney, it is important to elucidate the nature of the arterial lesion by aortography for two reasons. First, the procedures of measuring volume and sodium concentration of the urine obtained simultaneously from both kidneys provides only a comparison of the arterial blood supply to the two kidneys. It is obvious, therefore, that a reduction in the volume and sodium concentration of the urine from one kidney does not guarantee the integrity of the blood supply to the opposite kidney. Therefore, one cannot confidently proceed to remove a kidney when differential function studies suggest impairment of its arterial blood supply, without first demonstrating that the artery to the opposite kidney is normal. A second advantage of renal angiography is the possibility, in young persons, of demonstrating unilateral renal artery lesions which can be repaired by the vascular surgeon, thereby alleviating hypertension without loss of a kidney.

Recently at another Toronto hospital a case of hypertension was found to be due to a infarct of one kidney. This case showed no significant difference in the volume and sodium concentration from the two kidneys. Because of experience with this case Yendt suggests that aortography should also be done when the clinical picture is suggestive of renal infarction even though differential renal function tests are normal.

During the course of their differential sodium concentration studies, Yendt and associates were intrigued by the fact that in many cases in which there had been some leakage of urine around the ureteral catheters, the sodium concentration of this bladder urine was greater than that from the catheters. As a result of this fundamental observation in humans, further investigations at this University by Drs. Rappaport and Nicholson using experimental animals, have proven that electrolytes can be transferred across the bladder wall. This is an excellent example of how clinical research can sometimes lead to information about basic human physiology.

A large number of patients with recurrent renal calculi are being studied on a long term basis. By careful investigation of blood and urine chemistry as well as complete analysis of the calculi, it is hoped that some metabolic disturbance may be found in these patients.

A number of separate and distinct lines of research are proceeding in relation to parathyroid activity and the renal handling of calcium and phosphorus. Because serum calcium and phosphorus levels are often borderline in cases of hyperparathyroidism, several procedures have been advocated by various workers as aids in the diagnosis of this disease. These aids include the intravenous calcium test, the phosphorus deprivation diet, and indices based on the way the kidney handles phosphate. Workers at Toronto have been critically assessing these aids and have found that careful measurement of serum calcium and phosphorus levels is still the best means of establishing the diagnosis of hyperparathyroidism. In this work, advantage was taken of a rapid accurate method for the determination of serum calcium developed at this university by Dr. W. R. Campbell. More basic studies into the mode of action of parathormone have been started in patients to whom the hormone has been administered, and in patients who are being given either a

phosphate loading or a phosphate deprivation diet. A new method of determining serum ionized calcium which was recently developed in England is being evaluated by Toronto workers.

At the Hospital for Sick Children workers are investigating new methods of treatment of vitamin D refractory rickets, which is thought to be due to a congenital defect of the renal tubule to conserve phosphate. The standard treatment has been massive doses of vitamin D. However, clinical improvement following this therapy has often been disappointing due to marked hypercalcemia before serum phosphate rises to therapeutic levels. With this basic knowledge, they tried treating these patients with massive doses of orally administered phosphate whereupon a marked improvement was noted. It was also found that simultaneous large doses of phosphate probably reduced the amount of vitamin D needed to achieve a satisfactory clinical response in these patients.

Dr. Laidlaw and his associates at the Toronto General Hospital have shown that the rise in plasma levels of hydrocortisone during pregnancy is due not to increased secretion by the adrenal cortex but largely to a diminished ability of pregnant women to metabolize hydrocortisone. He has shown that hydrocortisone is more tightly held to plasma proteins in the intravascular compartment of the pregnant patient. This retention and the persistance of the normal diurnal variation in plasma levels probably explain the fact that Cushing's syndrome does not develop in pregnant women although their morning plasma hydrocortisone level is often as high as is found in patients with this disease.

CARDIOVASCULAR AND RESPIRATORY DISORDERS

An extensive investigation of the relative value of various procedures in the diagnosis of pulmonary emphysema has been made here in Toronto. The inferior right lung border was determined by percussion in the mid-clavicular line in 192 subjects, and was shown to be at or above the sixth interspace in normal subjects and in patients without emphysema. Patients with emphysema usually had right lung borders below the sixth interspace, but if significant pumonary fibrosis was present, then the right lung border was often within the normal range.

"Surprise" roentgenograms were taken of 54 subjects who were breathing normally. If the level of the right diaphragm on this roentgenogram was at or below the eleventh rib, then emphysema was probably present. If the diaphragm was above this level, emphysema could not be excluded.

Dr. C. R. Woolf and his associates, at the Toronto General Hospital have begun an interesting and challenging study of the objective assessment of dyspnoea of cardiac origin. The sensation of breathlessness is undoubtedly a complicated phenomenon about which very little is known. It is a subjective complaint and liable to the influences of emotion, ignorance, fatigue, and other factors. The study of this problem is beset by many technical difficulties, not the least of which is the inability to record or study the sensation in an objective manner.

Dyspnoea can be caused by primary pulmonary or cardiovascular diseases and may exist in the absence of either. When dyspnoea is the result of primary pulmonary disease one or more of the commonly used pulmonary function tests will be abnormal. These tests include measurements of minute volume, vital capacity, maximum breathing capacity, functional residual capacity, the A-a gradient and the oxygen content of arterial blood. Cardiac disease in contrast to primary lung disease, causes no change in arterial blood gases (except in certain forms of congenital heart disease or when pulmonary edema is present), little or no changes in residual volume and a relatively small reduction in maximum breathing capacity. If congestion

of the vascular bed exists, such as in mitral stenosis, the total volume of the lung may be decreased. There is no increase in residual volume and no alteration of alveolar ventilation. As a result of persistent pulmonary artery hypertension, the small vessels of the pulmonary system undergo changes that may lead to some restrictions in the pliability of the lung tissue. As a result, the maximum breathing capacity may be reduced. In some cases a barrier to the transit of oxygen across the alveolar capillary membrane has been found. Because a patient with cardiac dyspnoea may have all or many of the simple pulmonary function tests within normal ranges, many puzzling questions arise. More positive objective measurements of respiratory function are needed for the proper assessment of patients with cardiac and respiratory embarrassment.

Dr. Woolf and his group are approaching this problem from several angles. They have tried to measure and compare the speed of diffusion of gases across the alveolar capillary membrane in normal people and in patients with various types of cardiac disease. Secondly, they are trying to ascertain whether cardiac dyspnoea bears any relationship to carbon dioxide; whether the respiratory centre of these patients is more sensitive to changes in carbon dioxide tension; and since cardiac dyspnoea almost invariably occurs first during exercise whether there is an abnormally high carbon dioxide tension during exercise. Thirdly, complex methods are being used to objectively measure the "work of breathing" in both normal and dyspnoeic patients. Those diseases that weaken the neuromuscular system, reduce mobility of the thorax or flexibility of the lung, or increase obstruction to transbronchial air flow may induce dyspnoea chiefly by increasing the "work of breathing". The work of breathing is mainly concerned with overcoming the elasticity of the lung and with moving gases through the pulmonary tubes. Dr. Woolf is assessing the value of measuring the "work of breathing" in both normal people and cardiac patients. A large body of data is available on sixty cardiac patients; the results are at present undergoing statistical analysis and conclusions are not yet available.

A number of pulmonary and cardiac function tests requiring an ear oximeter have been devised. The oximeter will record continuously the percentage of oxygen saturation of blood in the ear; this will correspond closely to the arterial oxygen saturation if the ear capillaries are dilated by warmth or application of a rubefacient ointment. Members of the Cardio-Respiratory unit of the Toronto General Hospital have reported on the usefulness of this test in certain cases of congenital heart disease and also in various pulmonary disorders. A prolongation of the fall of the arterial oxygen saturation (desaturation) when patients with diffuse pulmonary emphysema were changed from breathing oxygen to breathing air, was observed and was probably due to inefficient gas mixing. The desaturation time was a useful, rapid test for the presence of diffuse emphysema and was reproducible with reasonable accuracy. Patients with other types of pulmonary disease such as bronchiectasis and restrictive ventilatory defects had a normal desaturation time.

Most normal subjects showed a fall in arterial oxygen saturation during a one-minute 30-step exercise test. In patients with alveolar-capillary block, severe ventilation defects, and moderate to severe emphysema, the fall was considerably higher than in the normal subjects.

Oximeter tests were found most useful when combined with simple tests of ventilatory function. Under such circumstances a diffusion defect was indicated by normal or near normal ventilatory function but abnormal arterial oxygen desaturation on exercise. The presence of emphysema was confirmed by a prolonged desaturation time; the severity of

a ventilation defect might be judged by the effect of exertion on the arterial oxygen saturation.

The ear oximeter can serve two purposes in the investigation of congenital heart disease. It can provide a continuous record of arterial oxygen saturation and it changes in response to varying situations; it can inscribe a dye dilution curve of the central circulation following intravenous injection of dye, from which the direction and magnitude of intra-cardiac shunts can be estimated.

Toronto workers have recently published a report on the diagnostic use of the ear oximeter in congenital heart disease while the subject is breathing pure oxygen. They have shown that a decrease in arterial oxygen saturation during a standard exercise test while the subject is breathing pure oxygen occurs in the presence of central veno-arterial shunt, but not in acquired heart or severe pulmonary disease. The oximeter tests have been valuable in detecting intracardiac shunts, in particular right-to-left shunts in the presence of a normal arterial oxygen saturation at rest. They have distinguished the cyanosis of right-to-left shunt from the cyanosis of pulmonary disease and acquired heart disease.

Intracardiac phonocardiography as a diagnostic technique in heart disease has been extensively investigated in the cardiovascular unit of the Toronto General Hospital by Dr. George A. Feruglio. With the aid of a barium titanate microphone incorporated in the tip of a specially designed catheter, intracardiac phonocardiograms were recorded from both the right and left side of the heart in patients with either congenital or acquired heart disease. It has been suggested that the technique, by providing precise localization of the source of heart sounds and murmurs, would not only increase knowledge of the site and mechanism of production of these sounds, but would also be an important aid in diagnosis. Intracardiac phonocardiograms were recorded routinely with an electrocardiogram as a reference tracing and with a simultaneous chest phonocardiogram for comparison studies. The phonocatheter could be clearly seen by means of fluoroscopy because of its metallic components.

Special attention was paid in the investigation to the fact that in intracardiac phonocardiography, sounds and murmurs, even loud ones, are sharply localized in one chamber or vessel and are not recordable in any other neighbouring cavity. This problem is still under investigation. At present it can only be said that even by using full amplification in the recording system, murmurs could not be recorded in any other chamber except that which received the blood flow responsible for their production. Therefore, in the presence of uncomplicated ventricular septal defect, a pansystolic murmur is recorded only within the right ventricle; in cases of patent ductus arteriosus a continuous murmur is recorded only within the pulmonary artery. Both these conditions could be diagnosed or excluded with certainty even when oxygen studies and clinical signs were equivocal. In cases of pulmonary stenosis an ejection murmur was recorded only within the pulmonary artery and its branches. Infundibular and valvular pulmonary stenosis showed different patterns during withdrawal of the sound catheter into the ventricle. In atrial septal defect it was confirmed that murmurs and sounds are produced by the increased flow across the tricuspid and pulmonary valves, rather than by flow across the defect. In cases of tetralogy of Fallot, no murmurs were recorded within the right ventricle and only a very soft ejection murmur was present in the aorta. This confirms the fact that the defect of the interventricular septum in this condition is usually silent, and that the loud ejection murmur recorded within the pulmonary artery is alone responsible for the harsh systolic murmur audible over the precordium. In cases

of isolated ventricular septal defect, a pansystolic murmur, sharply localized within the right ventricle was a diagnostic sign even in cases in which oxygen or dye dilution studies were doubtful, or suggested the presence of an interatrial or aorto-pulmonary shunt, rather than an interventricular one.

When the results obtained in acquired heart disease were analyzed, it was shown that intracardiac phonocardiography has only a few practical applications, such as establishing the tricuspid origin of the apical systolic murmur in pure mitral stenosis (due to relative tricuspid insufficiency), in differentiating between a mitral opening snap and a delayed pulmonary closure (by means of simultaneous recordings from within the pulmonary artery and externally from the mid-precordium or the apex), and in defining right-sided gallop rhythm.

Dr. R. W. Gunton and his associates have been investigating the mechanism of shock following myocardial infarction, which has always been a serious and distressing complication because of its relatively poor response to all forms of therapy. They have found that a reduction in cardiac output is the primary defect responsible for the hypotension and that the peripheral resistance seems to be greatly increased in most cases. In accordance with this finding it was shown that vasopressor drugs such as norepinephrine, which have been frequently used in the treatment of this condition, did not significantly reduce the mortality.

CONCLUSION

We hope that we have not only presented some new and valuable information to you but that we may have established a little more insight into the everyday challenges, frustrations, and achievements of the research worker. In many ways it is unfortunate that students do not have more direct contact with medical research during their undergraduate years. For several reasons this is not practical at our university at the present time. Most students cannot afford to spend time away from their regular studies during the school year, nor can they afford to forego a higher-paying job during the summer months to take a temporary research post. Most research workers feel that the summer months do not allow sufficient time for a student to properly conduct a project on his own and without this direct exposure the student only becomes acquainted with research in the most superficial way.

At certain medical schools such as Harvard, where they have elective terms, students take an active part in the research programmes. During the early medical years, projects are started in an "off term" and are often carried through until graduation. During the school term they continue their project by spending some time each day on it. They are advised and encouraged by staff members. Advocates of this system point out that, early in his medical training, the student is exposed to "research discipline". He must look up and collect previous relevant information, he must design his experiments being careful to cover the control aspect as well as other factors, he must be thoroughly familiar with the limitations of the methods he is using, and finally he must interpret the results. These processes can best be learned if the problem is your own.

Most research workers agree that this disciplinary regime has much to offer the student. Early in his medical training he is forced into thinking clearly and making decisions in a relaxed atmosphere, rather than cramming facts and figures into his cerebral cortex from one exam to the next. It is a valuable think-

ing process which will influence and guide his future either as a research worker or as a family doctor. It teaches him how to accurately assess information and how to interpret laboratory data. Moreover, most students are probably better tuned temperamentally to undertake certain research projects than are graduates. At a time when the young graduate is highly absorbed in clinical diagnosis and treatment it is sometimes distasteful for him to spend a year subjecting rabbits or mice to various procedures if he plans a clinical career. Despite these many advantages, the basic problems still exist. Where does the average student find time in an already crowded curriculum to conduct a research project and how can the accommodation and funds be made available?

If the University of Toronto is to continue to be an integral part of international research, the ranks of her workers must be continually augmented by imaginative and ambitious young students who possess those certain qualities that mark the true scientist. We have tried to indicate in these articles the many opportunities that await these students who relish the challenges that only medical research can present.

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ANSWERS TO "ON INSPECTION"

FIGURE 1.

The instrument is a paediatric sphygmomanometer. Its particular feature is that it is also an oscillometer, a feature which enables one to take blood pressures without auscultating or palpating. Various cuff sizes are also shown. These range from the very small size used on an infant, to the large adult size. A cuff which is too narrow gives readings which are too high; one which is too wide gives readings which are too low.

Infants—cuff should not exceed 2.5 cm. ($\sim 1''$).
Young children—3 inches wide.
Average adult—5 inches wide.
Outsized adult—7 or 8 inches wide.

FIGURE 2.

The meningomyelocoele is obvious, but the encephalocoele should not escape your attention.

FIGURE 3.

This is an example of an extrophy of the bladder occurring in the male. It is one of the most distressing congenital malformations which the surgeon must treat. The bladder opening as it does on the anterior abdominal wall, allows a continual escape of urine which produces malodor and a disagreeable wetting of the clothing. The everted and exposed mucous membrane is very sensitive and is easily irritated by an overlying pad or dressing. The deformity is accompanied by a wide separation of the pubic bones, so that there is a waddling and unstable gait.

FIGURE 4.

When examined pathologically, this lesion showed haemorrhagic degenerative changes and cyst formation consistent with the diagnosis of an old haemorrhagic bursitis.

FIGURE 5.

Scoliosis. It is important to separate functional scoliosis, which is only a postural defect, and the simple nonprogressive structural cases, from the progressive structural ones which if untreated go on to a crippling deformity.

FIGURE 6.

This is a case of severe lymphedema, or elephantiasis. Any abnormality which results in severe lymphatic obstruction or stasis can cause this condition. These derangements include congenital weakness of lymphatic walls or valves, block dissection of lymph nodes and channels, x-ray obliteration of these channels or their occlusion by neoplastic cells or fibrosis following multiple attacks of lymphangitis and lymphadenitis. In tropical climates, a common cause is the filaria Bancrofti which settle mainly in lymph channels and glands and set up a chronic irritation.

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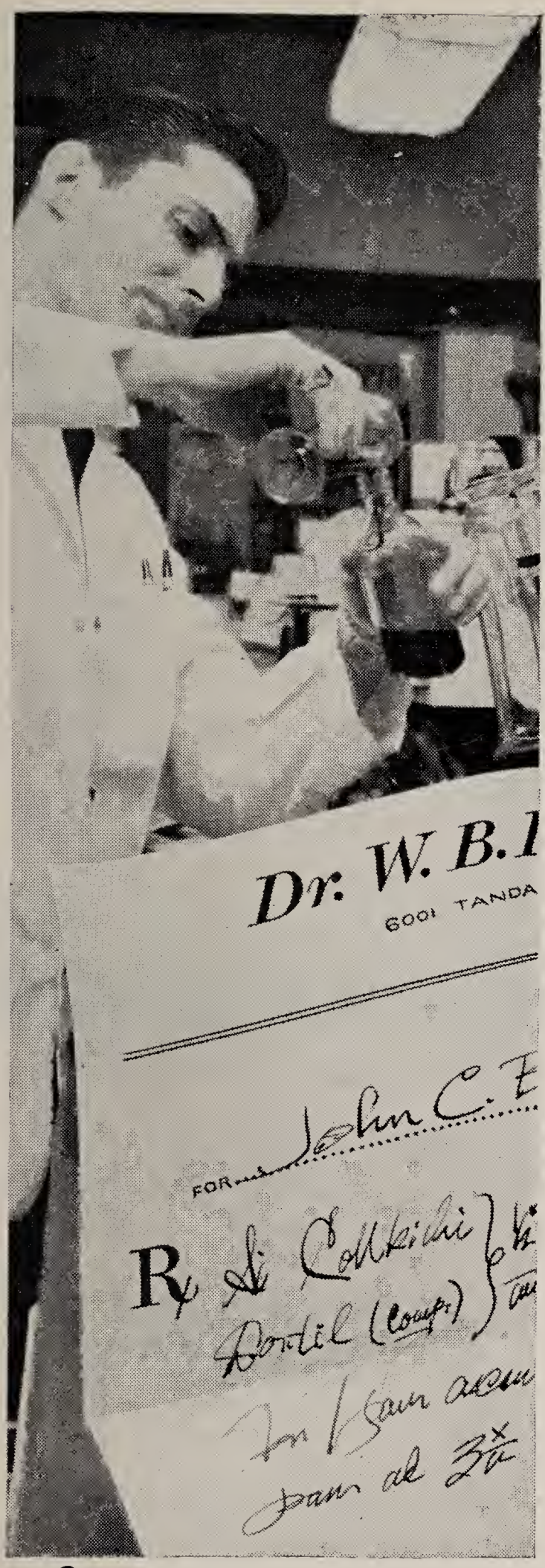

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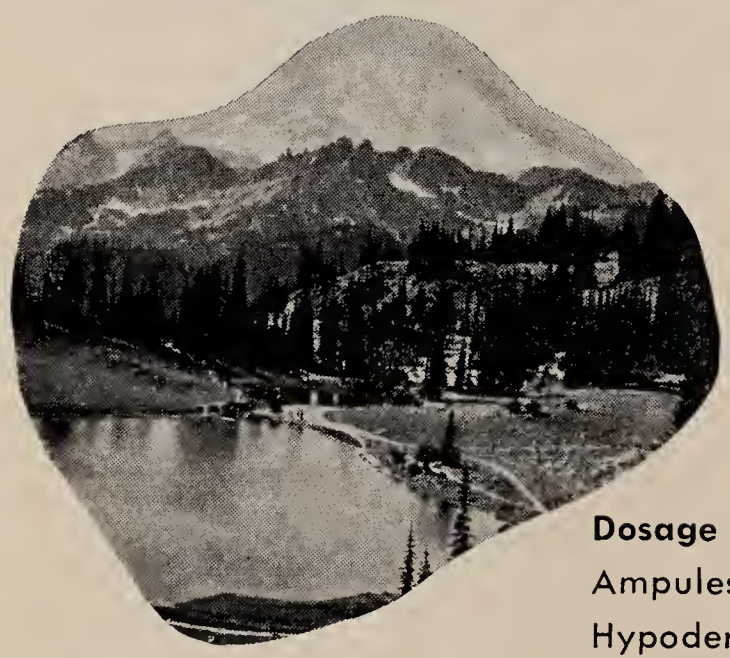

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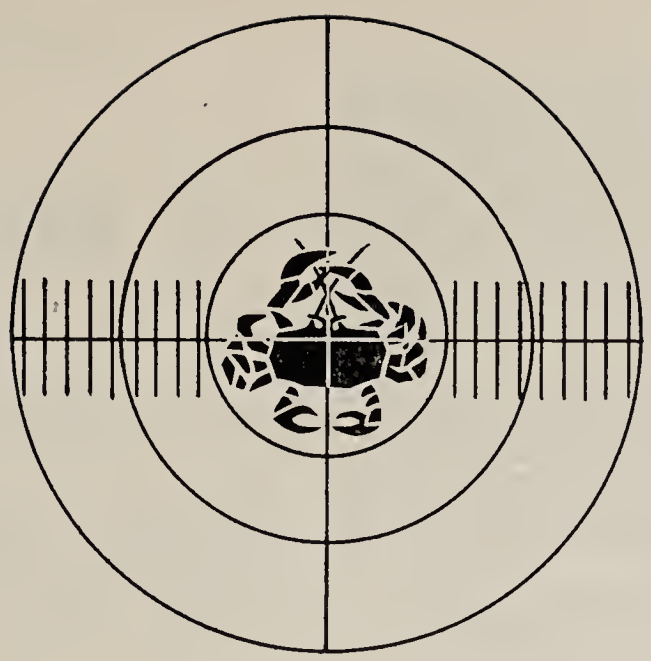

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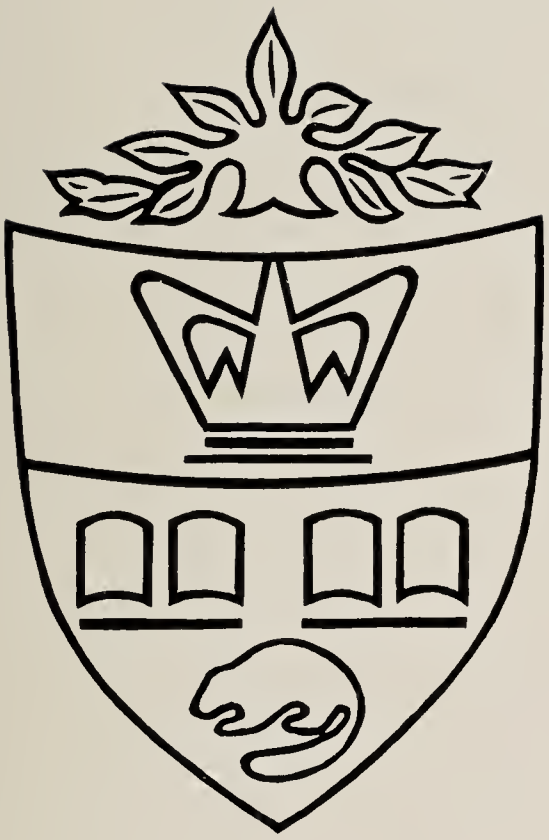

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